The molecular basis of occupational allergy.

Thesis

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THE MOLECULAR BASIS OF OCCUPATIONAL ALLERGY

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ABSTRACT

The problem of occupational allergy has only been highlighted in recent years. Diseases and disorders arising from acute exposure to large quantities of chemicals and concern over their potential toxic properties generally overshadow considerations of likely allergic reactions and the possibility of sensitisation developing. This thesis summarises the basic mechanisms of immunity and allergy and lists the substances which have given rise to sensitisation and allergic reactions in workers exposed to them. The literature covering allergy and sensitisation (including case histories of workers, animal studies and laboratory investigations) to particular organic chemicals encountered in occupational environments is reviewed. The mechanisms by which these chemicals stimulate allergic reactions in the body are discussed with particular reference to the chemical structure and molecular configuration of the chemicals. Basic physical data, structural formulae, the adverse reactions reported and related details are tabulated for each chemical. Occupational allergy to acid anhydrides is considered in more detail and typical case histories of sensitised workers given. The question of sensitisation generally is discussed. Recommendations for control measures to prevent or alleviate cases of occupational allergy, on improvements in the screening of workers and for the wider availability of information on the subject are made. Tests used in allergy investigations are summarised and a glossary of medical and related terms is given.

CONTENTS

INTRODUCTION

The presence of diseases and disorders in workers developing from and specifically related to their occupations has been recognised for centuries. As early as Roman times there was some awareness of the connection between occupations and diseases particularly in relation to metal miners and sulphur workers. In the seventeenth century[1] Paracelsus a physician, identified the miner's liability to lung disorders and the smelter's risk of poisoning by heavy metals. Ramazzini, the father of occupational medicine, published[2] a treatise in 1700 and not only identified many occupational disorders but also suggested ways of avoiding or reducing them. Knowledge and awareness of conditions related to particular trades or industries has continued steadily up to the present.[3]

However, the potential for exposure to hazardous chemicals today is greater than ever before. not only in the working environment but also in the home and during recreational and other leisure activities. In the present century, and especially since the Second World War, the rapid development and diversity of industry have created a marked increase in the numbers of organic and inorganic substances that are toxic or have potential as allergens or irritants.

Recent literature on incidents of occupational allergy and information regarding case histories is fragmented and of variable quality. Statistics on the prevalence of particular conditions are difficult to obtain with any degree of accuracy. One reason for this is that unlike many other occupational diseases, allergy per se is not a notifiable condition under current health and safety legislation in this country.

The subject of sensitisation and occupational asthma was reviewed by the Industrial Injuries Advisory Council in 1981 when seven groups of agents were studied. Principally as a result of the Councils[4] report occupational asthma was scheduled in March 1982 as a prescribed disease enabling workers suffering from permanent disablement caused by certain agents to claim industrial benefit.[5] Whilst only seven groups of agents are currently listed (see table 1) it is likely that further agents will be added in due course. Benefit is only available to workers suffering an irreversible condition and is not claimable in respect of short term disability. Accordingly only serious cases of the disease are reported and then only in retrospect. Furthermore occupational asthma can develop from non-allergic causes, especially through irritation, and it is such cases which are likely to be permanently disabling and therefore reported rather than those developing through allergy.

TABLE 1

OCCUPATIONAL ASTHMA

Prescribed causal agents under the Industrial Injuries Scheme.[5]

Isocyanates

Platinum salts

Acid anhydride and amine hardening agents (used in epoxy resin systems)

Fumes arising from use of rosin as soldering flux

Proteolytic enzymes

Dusts arising from barley, oats, rye, wheat or maize or meal or flour made from such grain

Animals or insects (used in research, education and laboratories etc)

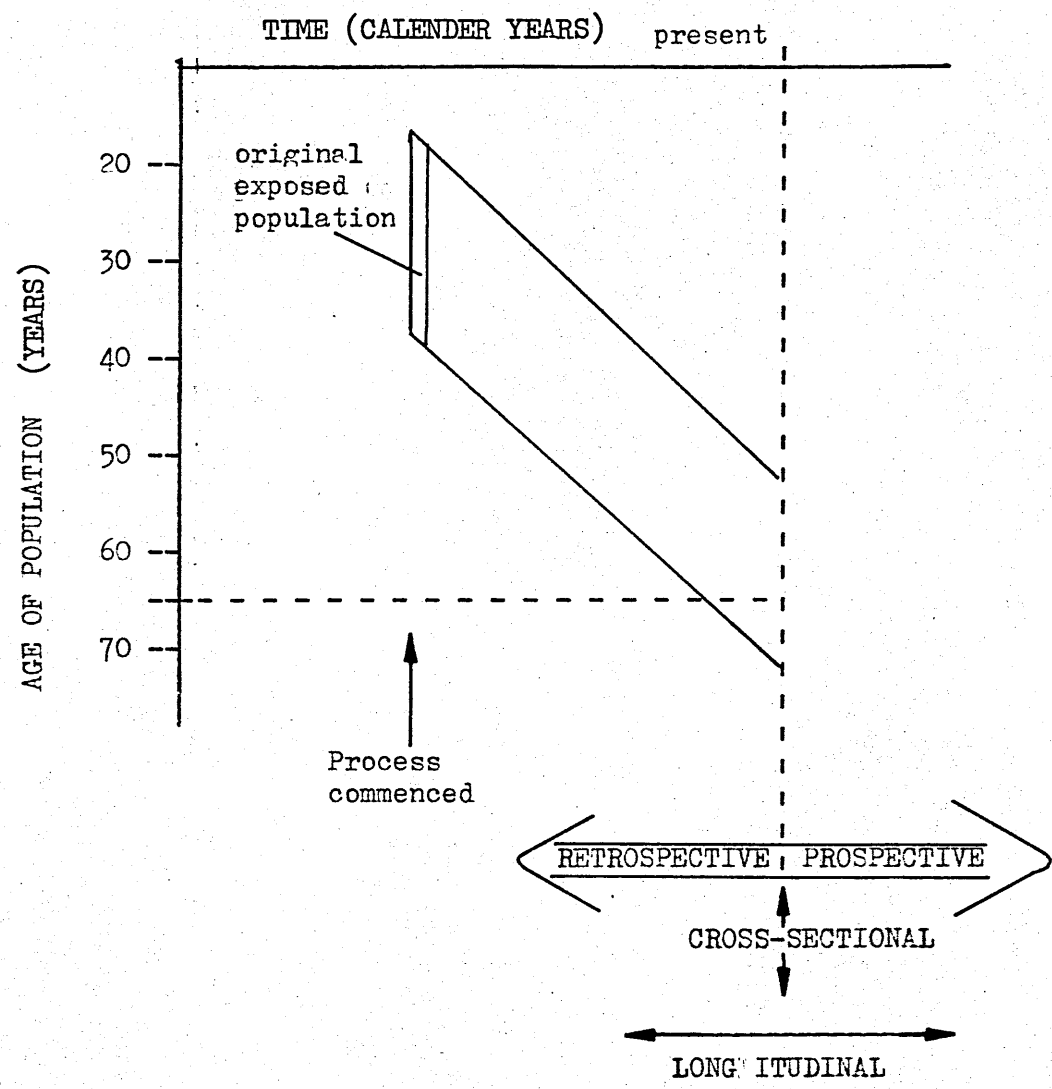
The Industrial Injuries Advisory Council is currently reviewing[6] the data on other known sensitisers with a view to extending the list of prescribed causal agents for which injury benefit can be claimed by chronic sufferers.

Much of the published data on occupational allergy (and respiratory allergy in particular) is derived from case histories of individual workers referred to specialists for diagnosis and treatment. Some surveys and epidemiological studies of groups of workers and whole industrial plants have been undertaken. A variety of study options have been used[7] including both cross sectional and longitudinal. retrospective, prospective and specific groupings. (See figure 1). Limited studies on animals particularly the guinea pig have also been undertaken. In many cases strong immunological evidence of an allergic mechanism causing symptoms in workers suffering adverse reactions to substances at work has been obtained but in others an allergic involvement can only be deduced or suspected. Clearly this reduces the reliability of the data when taken out of context.

The manner in which the respiratory sensitisation problem has surfaced in different occupations has varied considerably. Farmer's lung, Malt worker's lung and allergies in workers handling animals have been recognised for some time. The causal agents are known to be proteins or other macro-molecules present in moulds and other fungi growing on hay or barley and in the latter case, arising from animal waste products (dander).

FIGURE 1

STUDY OPTIONS IN OCCUPATIONAL EPIDEMIOLOGY [7]



Traditionally emphasis has been given to diseases and disorders (eg. asphyxia, burns, poisoning etc.) resulting from acute exposure to fairly high concentrations of such substances and the physical problems (eg. fire and explosion risk) presented by them. More recently concern has been directed towards more long term conditions (including asthma and various forms of cancer) likely to be caused by continued exposure to lower concentrations. Indeed routine toxicity testing involving animals has become established practice and is mandatory in certain cases.

The problem of occupational allergy however, remains relatively obscure and masked to a large extent by these 'more important' considerations. The limitations of current data, inability to establish unequivocal diagnosis in apparently sensitised patients, the low concentrations of chemicals involved and the small numbers of workers likely to be affected often mean that little priority is given to this subject in many industries. The lack of established animal tests to screen chemicals for the existence of sensitising effects on humans together with problems of identifying highly susceptible workers prior to exposure are additional factors. Dermatitis (which may be allergy related in some cases) is somewhat of an exception with positive steps being taken in most factories to eliminate or reduce incidents amongst exposed workers, although such precautions are often introduced for different reasons and prevention of dermatitis is a secondary consideration.

One of the first instances in industry was the sensitisation of workers involved in enzyme detergent manufacture which was also linked with skin problems amongst workers and consumers using these products.[8] Most recent attention has focused on a wide range of organic isocyanate materials used in industry. In the printing and packaging trades where isocyanate containing inks and adhesives have been widely used trade union pressure has led to substitution of many of these products. currently similar concern is being expressed over the use of isocyanates in the production of polyurethane foam and the spraying of polyurethane paints Allergy to inorganic compounds particularly platinum salts is also well established with 20-25% of the workforce in one U.K. plant alone known to suffer from the condition.[9] Workers in the pharmaceutical and animal feed industries are also high on the list of occupational allergy sufferers.

This dissertation is primarily concerned with respiratory allergies and other adverse reactions in man arising from substances released into the environment in industrial (and other occupational) processes focussing in particular on the molecular basis of such reactions. The substances concerned are principally reactive organic chemicals of relatively low molecular weight present in dusts, gases and vapours in working environments as a consequence of particular industrial or related processes. The adverse effects of inorganic chemicals, drugs/and of living organisms have been specifically excluded from this study.

administered for therapeutic purposes

IMMUNITY AND ALLERGY

2.1 Native and adaptive immunity

Immunity refers to the capacity enjoyed by an organism to remain unaffected by harmful agents in its environment and from those arising from within itself. The defence mechanisms responsible for this immunity are understandably complex and varied but two broad classifications are recognised:

a) Non-specific or native immunity - general body defences which kill or prevent the multiplication of micro-organisms or other parasites.

b) Specific or adaptive immunity - mechanisms that are activated individually after a microbe or other foreign material invades the body.

Native immunity is provided by several routes including the physical barriers of the skin and membranes and the filtering of nasal passages. Bacteriocidal enzymes in saliva, acidic substances in the stomach and chemical agents in the blood (eg properdin) and other tissue fluids capable of inhibiting or destroying microorganisms are all equally important. In addition all higher animals contain scavenging cells which ingest and destroy foreign particles. These are principally of two types, namely macrophages and granulocytes (polymorphonuclear leucocytes) both of which originate from cells in the bone marrow.

Granulocytes are highly motile cells containing granules (packets of powerful digestive enzymes and bactericidal agents) and are attracted by chemotactic agents and migrate to foreign material including bacteria which they ingest and digest. Macrophages also efficiently ingest foreign particles and digest bacteria but are slower moving than granulocytes.

A third type of cell(Eosinophils) which also originate from the bone marrow, have a phagocytic potential although their function is largely unknown. They accumulate at sites of antigen-antibody reaction in response to specific chemotactic factors liberated locally. Immune reactions involving IgE are particularly prone to attract eosinophils.[10] They are also implicated in the processing and cell to cell transfer of antigen breakdown products. In parasitic infections an increase in the number of blood eosinophils usually occurs.

A fundamental property of adaptive immunity is a highly specific memory, since the system actually learns from first interaction with a given agent. Furthermore the system has the ability to recognise materials that are foreign ie. to distinguish self from non-self. A remarkable and economical feature of the immune system is that recognition leads by one or more processes to inactivation.

Materials which can give rise to specific immune responses and interact with the cells and/or antibodies produced are termed antigens. Some foreign materials (generally of low molecular weight) are able to interact

specifically with pre -existing cells and/or antibodies but require to be conjugated with another material, usually protein, before being able to elicit a specific immune response themselves - these are known as haptens. In these cases it is the chemical reactivity of the molecule which is important not its size.

Recognition of a material as self occurs as a result of the material being present (at a suitable concentration) during the prenatal development of the organism. Additionally for material to be regarded as self it must be accessible to the cells of the immune system during development. The immune system of an organism will generally not respond against material regarded as self. This self-tolerance is achieved, during foetal development, by the removal or inactivation of certain cells of the immune system capable of reacting against the antigens of the body.

Tolerance to foreign antigens can also be achieved after birth through the administration of very small amounts of antigen repeatedly over a period of weeks or the administration of large amounts over a shorter period of time. The given antigen must be present in a form which allows it to persist in the circulation and not all be taken up by macrophages and related processes. The maintenance of tolerance must be a continuous process since the active principles of specific immunity are constantly changing and new cells and/or antibodies reactive to the given tolerated antigen may evolve which would initiate an immune response against it unless they are inactivated.

Most antigens have several distinct areas on their surfaces which are recognised as foreign and give rise to the specific responses against them, these areas are known as antigenic determinants. When two different antigens have one common antigenic determinant some of the antibody response made against one antigen will be able to react with the other, such antigens are known as cross-reacting antigens.

2.2 The Immune System and Specific Immunity

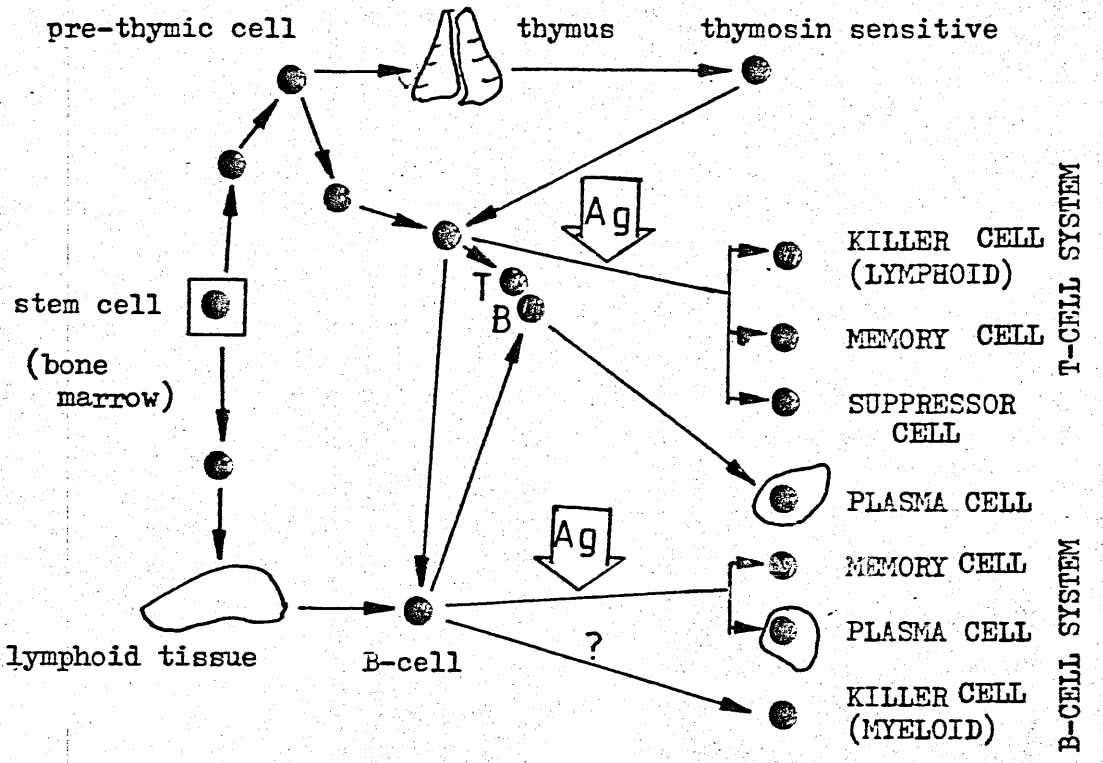
The immune response in specific immunity centres around a family of white blood cells called lymphocytes. In adult animals lymphocytes are derived from stem cells which are continuously formed in the bone marrow; these stem cells pass in the bloodstream from the bone marrow to specialist tissues known as lymphoid organs, eg. the thymus gland, spleen, tonsils, appendix, lymphnodes etc. The life cycle and behaviour of lymphocytes depends upon the location of the stem cells from which they originate, ie. whether they migrate from the bone marrow into the thymus gland or into other lymphoid tissues. Although all lymphocytes are similar in appearance they acquire characteristic components in surface membranes and differences in behaviour depending on the lymphoid tissues to which they relate. (See figure 2.)

The immune system can be regarded as two parts, humoral (antibody mediated) immunity and cell-mediated immunity, although there is interaction between the two systems in various immune responses. The two arms of the immune

FIGURE 2

DIFFERENTIATION OF LYMPHOCYTES[11]

A SCHEMATIC DIAGRAM OF THE FORMATION OF LYMPHOCYTES FROM BONE MARROW STEM CELLS AND THEIR DIFFERENTIATION INTO VARIOUS TYPES OF CELL INVOLVED IN THE IMMUNE RESPONSE.



system were discovered through experiments which tested:

i) whether a particular sort of immune response occurring in an individual could be transferred to a previously unimmunised individual by serum taken from the former and separated from his blood cells,

or ii) whether the reactivity could be transferred by the cells in the absence of serum.

Such experiments have made it possible to characterise many features of the two arms of the adaptive immune response in isolation from each other.

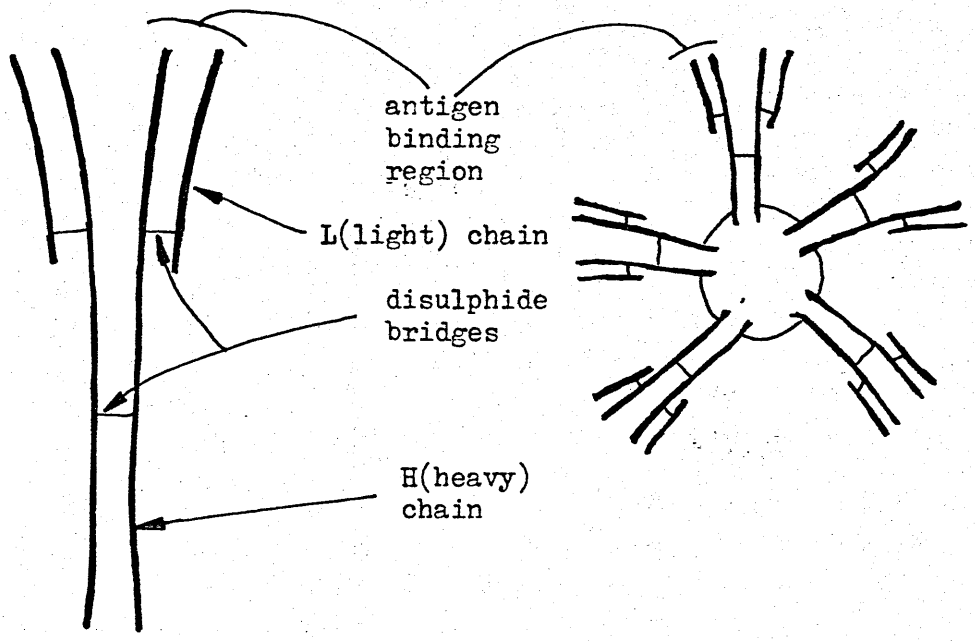
2.3 Antibodies

Humoral immunity is the arm based on soluble serum factors. Although there are many different reactivities in this category they have one prime feature in common - their specificity for particular foreign materials is dependant on specific antibody. For this reason reactivities within this area are termed antibody-directed immunity. Humoral antibody, namely the four principal types of immunoglobulins (referred to as IgA, IgE, IgG and IgM) are manufactured by cells of the B-cell system. (IgD is also produced but its role is not understood.) (See figure 3).

The clonal selection theory of antibody formation[12] (See figure 4) was developed in the 1950's by Burnet based on the selective hypothesis of Jerne. Circulating small B-lymphocytes carry highly specific receptors on their surface. Antigen selects from this preexisting array of cells and those

FIGURE 3

THE STRUCTURE OF IMMUNOGLOBULINS - THE ANTIBODY MOLECULE



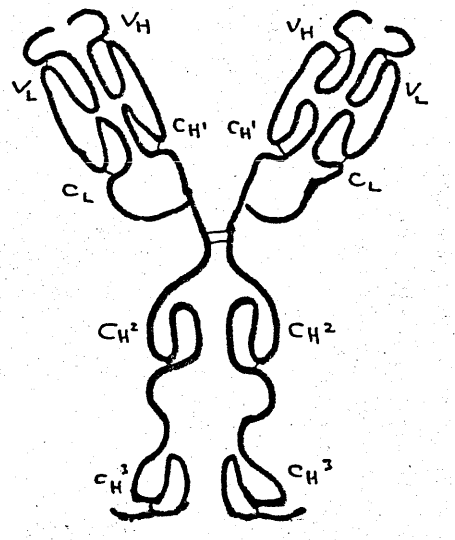
IMMUNOGLOBULIN G (IgG)
(molecular weight approx 150,000)

(IgM) IMMUNOGLOBULIN M
(mol. weight approx 1,000,000)

(IgD and IgE are similar to IgG in general structure; but have large H chains.
IgA is composed of multiples of the basic unit, often a dimer)

The H and L chains are glycoproteins.

FIGURE 3b. DIAGRAM OF THE IgG MOLECULE SHOWING THE LOCATION OF LOOPS (DOMAINS) IN THE PROTEIN BACKBONE



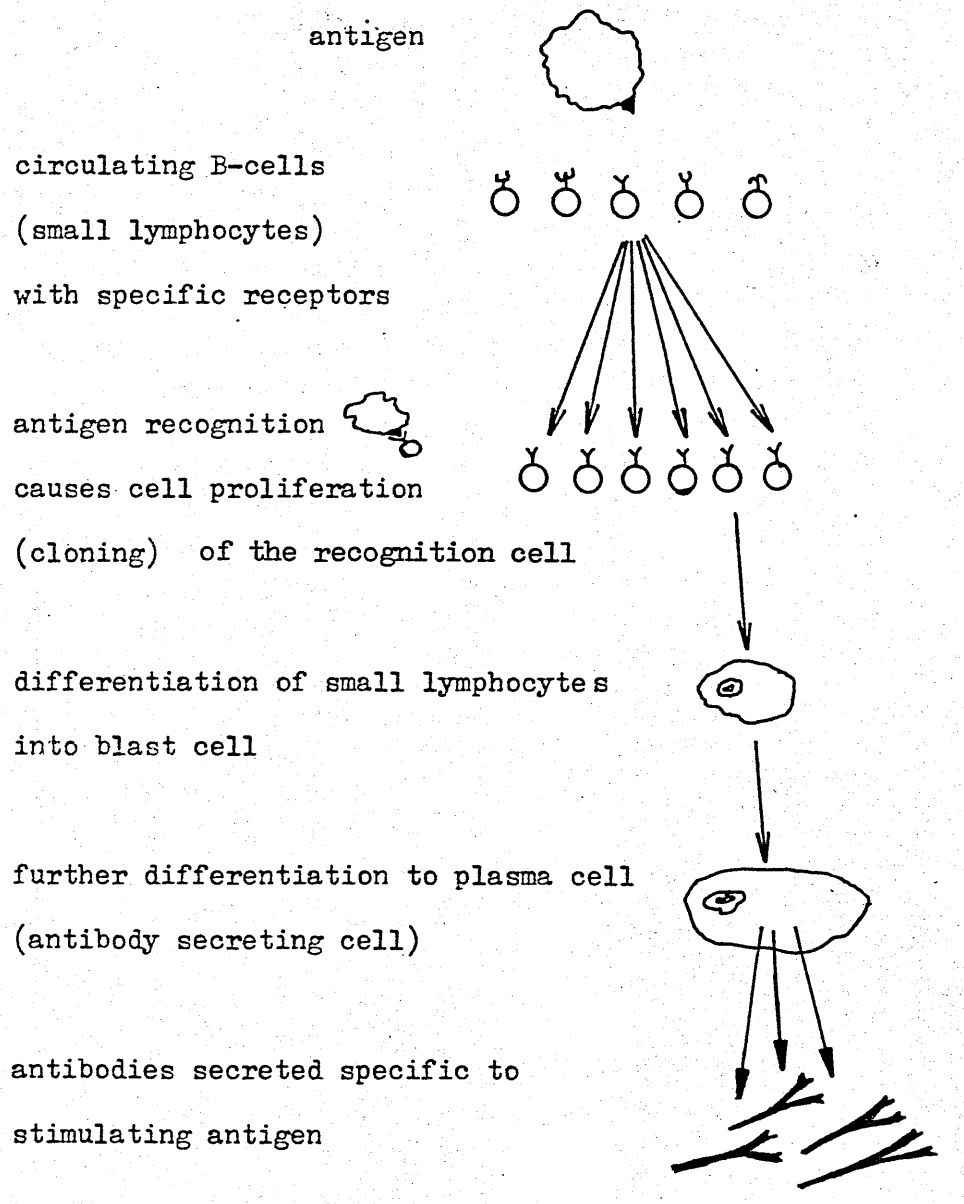
domain regions:

V_H variable heavy
V_L variable light

C_H1 constant heavy 1
C_H2 constant heavy 2
C_H3 constant heavy 3
C_L constant light

FIGURE 4.

ANTIBODY PRODUCTION - THE CLONAL SELECTION THEORY



having specific receptors to it are stimulated to divide and produce a clone of daughter cells. Some of these progeny are memory cells whilst others develop and mature into plasma cells, which have a particular ability to produce antibody at a high rate. The presence of memory cells enables a subsequent challenge with the same antigen to invoke a greater response than the previous encounter.

The commonest type of immunoglobulin (IgG) is distributed throughout the body in both the blood and tissue fluids and certain sub-classes are able to cross the placenta, thereby conferring immunity on the foetus. IgG is capable of activating complement and of initiating complement fixation (see below). IgM, a much larger molecule than IgG is found principally intravascular and is able to achieve greater complement activation than IgG. IgA is the principal immunoglobulin found in tears, milk, sweat, saliva and mucous secretions. It is found in the lining of the respiratory tract and the gut where it is capable of surviving hydrolytic conditions for significant periods. The fourth main type, (IgE) often referred to as reaginic antibody, is involved in immediate type allergic reactions. It has the ability to bind to the surface of mast cells[13] and induce the release of histamine and other pharmacologic mediators from these cells following antigen binding.

Antibody can affect antigen in three ways (See figure 5):-

a) Direct binding of the antigen by antibody (especially where the antigen is a virus or bacterial toxin) neutralises it and interferes

with its proliferation, movement and ability to attack other cells in the body- a process known as agglutination if the antigen is particulate.

b) Binding of antibody to antigen in the presence of complement (see later) enhances the lysis of cellular antigen and also facilitates phagocytosis by scavenging cells.

c) By directing and influencing the activity of certain cells in association with the binding of antibody to antigen. Specific antibody with receptors for macrophages or neutrophils may bind to antigen giving rise to enhanced phagocytosis of the antigen by the cell or in the case of cellular antigen to killer cell activity (ie) the target cell is directly killed by the macrophage or lymphocyte by means of a mechanism not presently understood. Antibody may also bind to mast cells or basophils prior to binding with antigen resulting in the release of pharmacologic mediators from the cells when binding to antigen takes place[14]. This latter mechanism is a key part of immediate type hypersensitivity.

2.4 Cell-mediated Immunity

Cell mediated (or cellular) immunity is the part of specific immunity where the reactivities are wholly a feature of the cells themselves in that they can be carried out in the absence of soluble antibody, and the specificity is directed by the actual cells. The small lymphocytes involved

are influenced by the foetal thymus either by contact with epithelial cells or by a diffusable substance elaborated by the thymus, or perhaps both, causing them to differentiate into various kinds of thymic lymphocytes (T-cells). (See figure 2). This normal response is important for normal protective mechanisms against specific organisms such as viruses, fungi, parasites and certain bacteria.

T-cells can affect antigen by three main routes (See figure 5) (probably only one effect is possible by any individual T-cell) namely:-

i) Direct attack on the antigen (target cell) - the killer cell effect.

ii) The elaboration of various factors which have a direct effect on the antigen.

iii) The production of lymphokines - factors which attract other cells by chemotaxis and influence them to attack the particular antigen.

2.5 Complement

Complement comprises a system made up of nine distinct components (all proteins) which are present in the blood and tissue fluid of animals. The complement system constitutes a sequence of trigger mechanisms well suited to enlarge and diversify the effects of an antigen-antibody reaction. One of the important properties of complement is its ability to cause lysis of sensitised cells (ie. cells which have bound antibody) especially bacteria, through disruption of the cell membrane. (See figure 6).

FIGURE 5.

SUMMARY OF IMMUNE REACTIONS TRIGGERED BY ANTIGEN AND THEIR EFFECTS

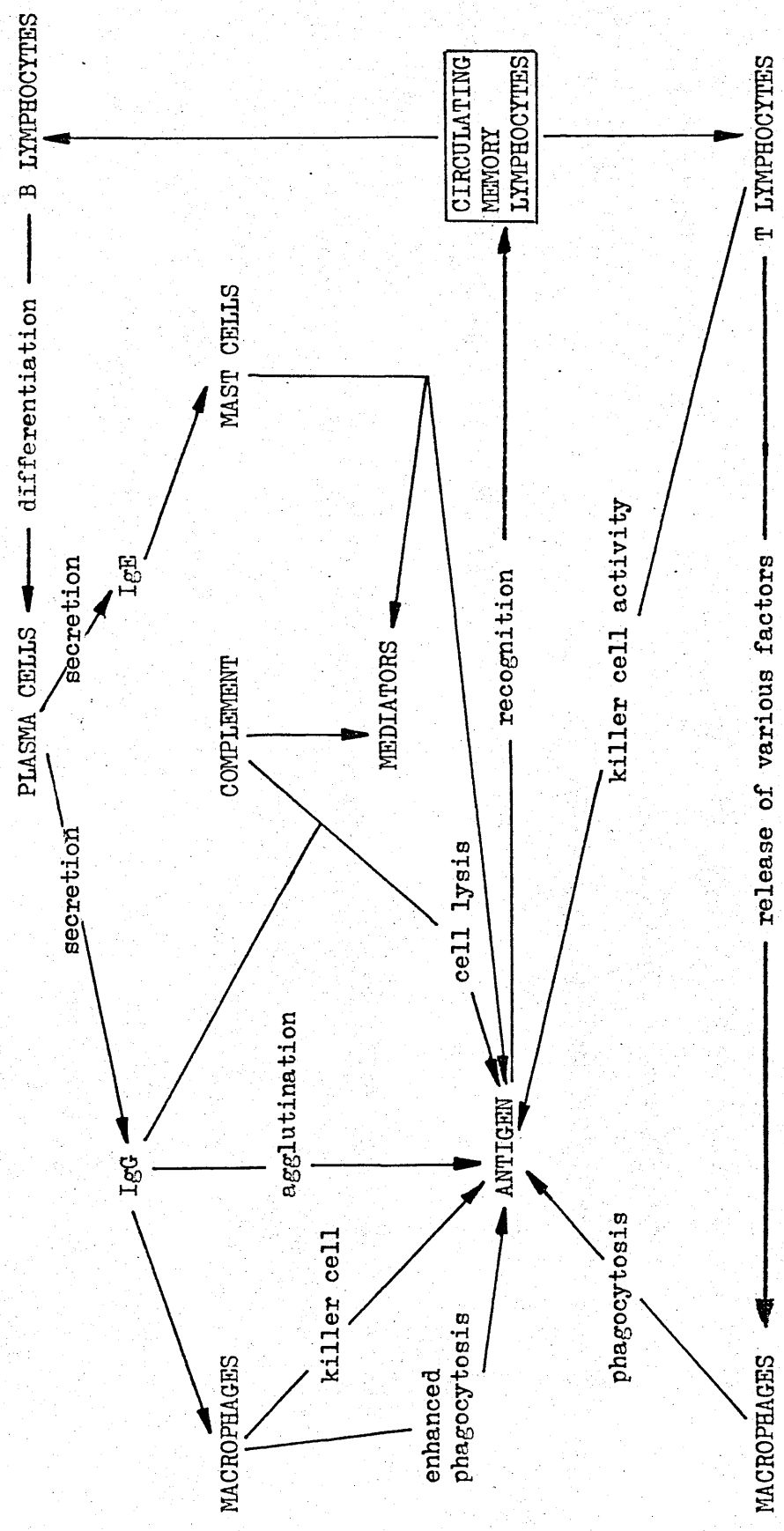
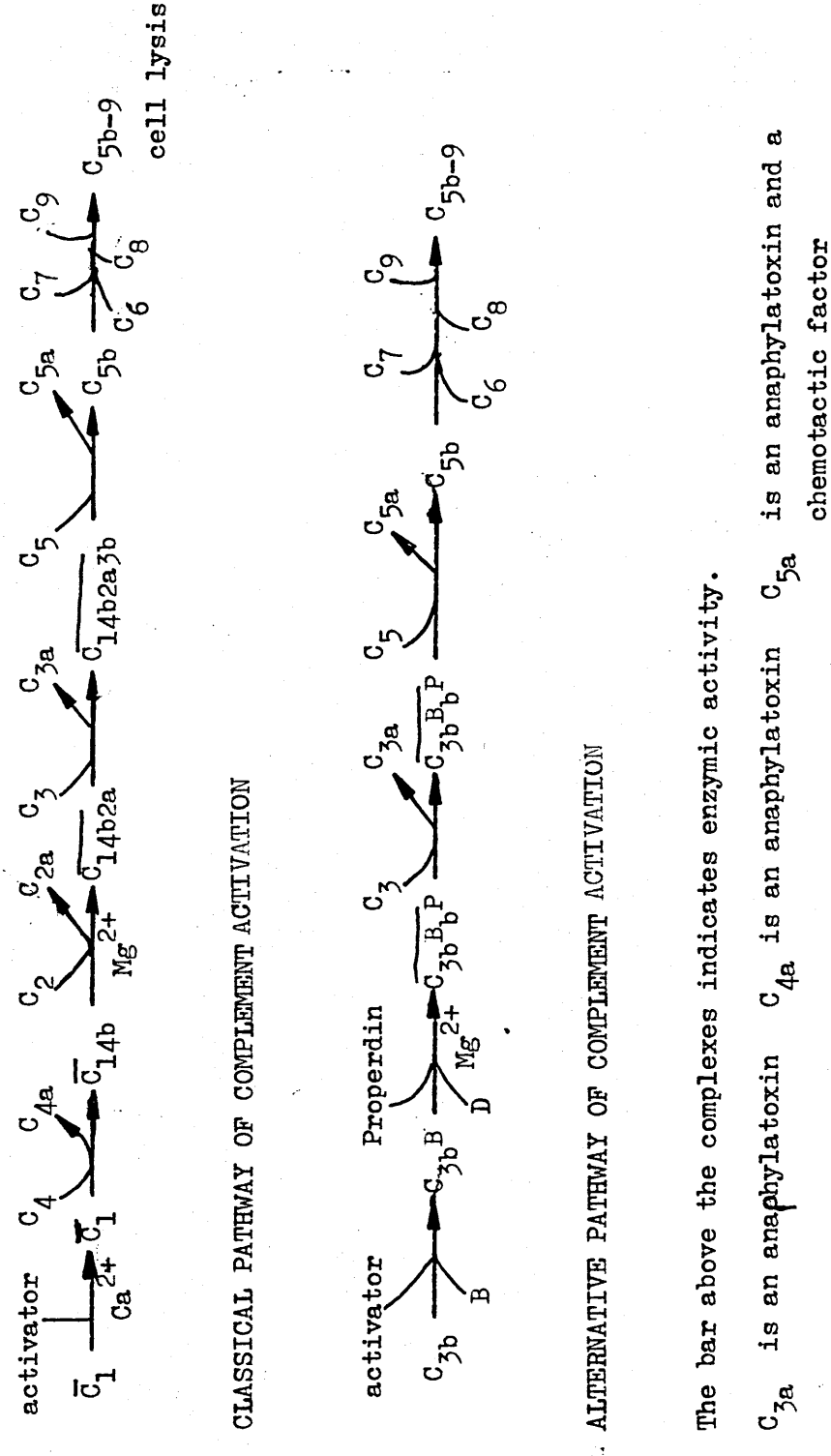


FIGURE 6.

THE COMPLEMENT PATHWAY : A CASCADE SYSTEM

A SYSTEM OF REACTIONS INVOLVING PROTEINS AND COFACTORS TRIGGERED FOLLOWING CERTAIN ANTIGEN/ANTIBODY REACTIONS AND/WHICH IN TURN GIVES RISE TO MANY OBSERVABLE BIOLOGICAL EFFECTS. THERE IS A LARGE ELEMENT OF AMPLIFICATION IN THE PATHWAY.



The bar above the complexes indicates enzymic activity.

C_{3a} is an anaphylatoxin C_{4a} is an anaphylatoxin C_{5a} is an anaphylatoxin and a chemotactic factor

Other important actions of the system include release of anaphylatoxin, a poly peptide, which initiates local muscle contraction and vasodilation (an anaphylactic type response); enhancement of immune adherence to cells (which facilitates ready ingestion and which attracts granulocytes to migrate to the site of the complex) and the stimulation of lymphokine production by lymphocytes.

2.6 Allergy

These systems which are normally immunoprotective can also be involved in immunopathologic processes where the system gets turned on and does not protect but is actually detrimental to the host. Four broad types of adverse reaction are recognised and are generally referred to as type I, II, III or IV according to a classification put forward by Gell and Coombes in 1968.[15] (See table 2.) The humoral antibody system is involved in three types of immunopathological reaction ie. types I - III reactions. In type IV or cell-mediated disease the T-cell system or cellular immune system is responsible for the reactions. Types I, III and IV reactions (which may be present in the subject at the same time) may be demonstrated by skin tests. While type II allergy has a skin presentation it is not looked for in normal routine skin testing.

The term Allergy (an altered capacity to react) was introduced in 1906 by von Pirquet[16] and applied to specifically induced reactions which were either enhanced or depressed. The word is nowadays used to mean altered reactivity which is increased above normal in response to an external

TABLE 2 : TYPES OF ALLERGIC REACTION - THE GELL AND COOMBS CLASSIFICATION.[15]

GELL AND COOMBS CLASS	I	II	III	IV
SYNONYMOUS DESCRIPTIVE TERMS	ANAPHYLACTIC OR IMMEDIATE HYPERSENSITIVITY	CYTOTOXIC	ARTHUS OR IMMUNE COMPLEX	CELLMEDIATED IMMUNITY OR DELAYED HYPERSENSITIVITY
PRIMARY LYMPHOCYTE INVOLVED	B	B	B	T
OTHER CELLS INVOLVED	MAST (BASOPHIL) CELLS AND EOSINOPHILS	POLYMORPHONUCLEAR CELLS		LYMPHOCYTES AND MACROPHAGES
IMMUNOGLOBULIN INVOLVED	IgE poss IgG	IgG, IgM	IgG, IgM	NONE
COMPLEMENT INVOLVED	NO	YES	YES	NO
EXAMPLE OF ANTIGEN	GRASS POLLEN; CONJUGATES OF PENICILLIN WITH CERTAIN PROTEINS	CIRCULATION SURFACE ANTIGENS	THERMOPHILIC ACTINOMYCES	TUBERCULIN PROTEIN p-DINITRO CHLOROBENZENE OTHER REACTIVE CHEMICALS
TIME SCALE SKIN TESTING TYPE OF REACTION WITH CELLS INVOLVED	20 MIN WHEAL & FLARE MAST CELL OR BASOPHIL	- NOT DONE	6 - 8 HRS ERYTHEMA & INDURATION (ARTHUS REACTION)	24 - 48 HRS ERYTHEMA & INDURATION MONONUCLEAR CELLS
IN VITRO TEST	R.A.S.T OR HISTAMINE RELEASE FROM LEUCOCYTES	CYTOLYSIS OF CELLS	PRECIPITIN REACTION	LYMPHOCYTE BLAST TRANSFORMATION BY ANTIGEN

noxious antigenic agent. Hypersensitivity, which implies a specifically increased capacity to react, is often used interchangeably with the term allergy. The antigenic agent which is capable of inducing a state of allergy in some persons is termed an Allergen.

An allergic reaction involves two (or more) contacts with the allergen:

i) an initial encounter by the individual of the allergen in which no reaction is apparent but as a consequence of which he is sensitized,

ii) a later encounter with the same material which triggers the allergic state causing a strong adverse reaction.

It is the process of sensitization which distinguishes allergy from irritation. Whilst the observed effect after encounter by a given allergen may be similar to that following encounter by an unrelated irritant the latter effect is not dependant on previous exposure of the individual to the substance concerned and does not involve the individual's immune system.

It is clear that many substances possess both antigenic and irritant properties and that the observed response following exposure to these substances results from several reactions. The physical, chemical and biological properties of the substance (especially its concentration), the route and other circumstances of exposure, together with the immunological reactivity and previous medical

history of the person exposed will influence the particular response observed.

The metabolism of a given substance by the individual concerned is an additional factor. The body generally treats foreign substances as undesirable materials which must be excreted as soon as possible. The chemical transformation of the substance by degradation or enzymic metabolism (including hydroxylation, conjugation, reduction or oxidation) to create a more polar (ie. more water soluble) compound or compounds and thereby facilitate excretion is primarily carried out in the liver. The metabolite or metabolites produced may be immunologically significant especially if they have an ability to react with proteins or other macromolecular structures. Obviously a supply of these susceptible carrier molecules is essential for the metabolites, acting as haptens to form antigens; however, proteins synthesised locally within the liver are ideally suited to combine with newly formed reactive metabolites.

The traditional criteria[17] for regarding a reaction as allergic (with or without supporting immunologic evidence) are as follows :

i) There is a history of previous exposure (without symptoms)- the period of sensitisation

ii) The degree of specific sensitivity may increase with further exposure

iii) A proportion, usually low, of exposed subjects are affected.

Generally allergic responses are elicited by dosages far less than those capable of sensitisation which in turn are usually far less than those capable of irritation. (See table 3). Furthermore allergic responses occur only in a small proportion of persons exposed to the substance at a given concentration whereas responses to irritation are more likely to affect most exposed subjects and all are unrelated to previous exposure.

Atopic individuals[18] appear to have a genetically determined capacity to produce specific IgE antibodies readily in response to the immunologic challenge presented by the ordinary, usually limited, exposures in daily life to common allergens. They show[19-21] a higher incidence and a far more rapid sensitisation to occupational agents than do non-atopic subjects.

An individual's immunological reactivity[22] such as the affinity or avidity of antibodies produced and the capacity of complement to modify the solubility and handling of immune complexes may also have a bearing on responses. Affinity is the description of the interaction between a single antibody site and antigen (or hapten) - the higher the affinity of a given antibody the lower the concentration of antigen (or hapten) required to cause half of the antibody-binding sites to be occupied. Avidity relates to how well antibodies and antigens stick together and is dependant on additional features such as the number of binding sites the antibody molecule has for antigen and the number of determinants on the antigen.

TABLE 3

EXAMPLES OF THE

RELATIVE QUANTITIES OF REACTIVE CHEMICALS INVOLVED

IN IRRITATION, ALLERGIC REACTIONS AND SENSITISATION.

Data for
Toluene diisocyanate fumes[23]

Irritant	> 0.5ppm
Allergic	0.005 to 0.02 ppm

Data for
Platinum salts[136]

Irritant	10^{-6} to 10^{-9} g
Allergic	10^{-15}g (approx 100,000 to 200,000 molecules)

2.7 Allergic Reactions

The response following reaction between allergens and sensitised cells is influenced by the particular mechanism triggered. The clinical manifestations observed in allergic reactions are not specific to the allergen involved.

In the immediate reaction (type I) IgE antibody bound to the surface of circulating basophils and to mast cells reacts with antigen and leads to structural changes in the cells (degranulation) and release of pharmacological mediators. These chemical messengers, in particular histamine and SRS-A (slow reacting substance of anaphylaxis) act directly on local tissues and organs such as the capillary network, blood vessels, secretory glands and nerve cells. Histamine causes vasodilation in vascular tissue and increased permeability to plasma proteins thereby leading to inflammation, and contraction of smooth muscle leading to bronchoconstriction. SRS-A also contracts smooth muscle. Other mediators including prostaglandins and bradykinin also have vascular effects. IgE would seem to be a very rapid method for mobilising defence mechanisms locally. It is unlikely that IgE has a significant role in any other way since the quantities apparently involved do not appear sufficient to neutralise or agglutinate antigen.

Type III allergic reactions involve circulating antibodies (primarily IgG) reacting with antigen in the blood stream forming immune complexes and activating the complement cascade. This in turn activates blood clotting mechanisms, liberates kinin and the release of proteolytic enzymes, permeability & chemotactic factors.

The involvement and role of mediators in late (type III) reactions has been less widely studied and is not fully understood. It is possible that some mediators could have pro-allergic or inflammatory effects in the immediate reaction but opposing effects in the late reaction (prostaglandins in particular show examples of this and appear to exert vascular effects at an early stage but effect cellular cAMP levels and other effects later.) Many cases of respiratory allergy in particular appear to involve both an immediate and a late reaction commonly referred to as a dual response.

The true delayed reaction (type IV) is mediated by cells of the T-cell system, through the mechanisms described in section 2.4. The tuberculin-type skin reaction as observed in patch testing with allergens is the commonest indication of a delayed type reaction mechanism. The response develops slowly and reaches a maximum at 24 to 48 hours.

There is however some evidence for a role for basophils and mast cells as well as serum antibodies in delayed responses.[24] Many delayed responses, including contact lesions, in animals and man are heavily infiltrated with basophils;[25] some delayed skin reactions can be blocked by inhibitors of vasoactive amines[24] (suggesting that mast cells or basophil mediators are involved in the pathology of the lesion) and contact sensitising agents can induce an antibody response including reaginic (IgE) antibodies.[26]

OCCUPATIONAL ALLERGY

3.1 Allergy and Work

Since allergic reactions may be precipitated by non-occupational agents, (just as all adverse effects of an occupational agent may not involve sensitisation), in view of the long latent period of exposure (over ten years in many cases) and the likelihood that other workers are not affected, the basic causal agents may go unsuspected and domestic or recreational environments may be implicated instead. Bernadino Ramazzini (a professor of medicine in Italy in the eighteenth century) was the first to publish[2] a systematic account of trade diseases and highlighted the need to ask patients the important question 'What is your occupation?' when undertaking clinical investigations.

Improvement in or cessation of symptoms at weekends or during holidays or following changes in work locations or occupation generally indicate an occupational origin for the disease. Furthermore the rapid return of symptoms on resumption of work may suggest an allergic mechanism.

Allergic reactions caused by occupational agents giving rise to effects on the skin, the eyes or the respiratory tract have all been observed. Adverse reactions of the gastrointestinal tract also occur in food allergies, but are of little significance in occupational allergy. Whilst the observed reaction may indicate the organ or system in first contact with the agent this is not always the case (eg. respiratory disorders may result from general skin

contact with the agent or skin disease may follow from ingestion).[27-30]

3.2 Respiratory Allergy

Adverse reactions of the respiratory tract include allergic rhinitis (eg hay fever), asthma and extrinsic allergic alveolitis (referred to as hypersensitivity pneumonitis in N. American terminology.) Although rhinitis is fairly common in the general population it has little significance in occupational allergy.

Asthma[31], (defined as reversible obstruction of the bronchi and bronchioles) occurs in a wide variety of reactions which fall into two main categories, as described below. It can be caused by several factors unrelated to sensitisation including irritation. Immediate asthmatic reactions develop within minutes and can usually be associated with a particular causal agent. They rapidly reach a maximal effect and last about $1\frac{1}{2}$ to 2 hours. These reactions can be reversed by inhaled bronchodilator drugs and can also be blocked by the prior administration of sodium cromoglycate. Corticosteroids do not block the reaction. A type I reaction mechanism is thought to be involved.

The other group are termed non-immediate asthmatic reactions since they develop slowly and often imperceptibly. The reaction may develop after 1 hour and last approximately 5 hours or may come on after several hours reaching a maximum effect at 5 to 8 hours and last up to 24 hours. They can be blocked by sodium cromoglycate and are also

effectively blocked by corticosteroids. However, they respond poorly to bronchodilators. In this case a type III reaction mechanism is thought to be involved. A further non-immediate reaction, recurrent nocturnal asthma, develops in the early hours of the morning following exposure and recurs without further exposure at the same time each night for several nights. This reaction responds poorly to all of the drugs.

The chief features of Extrinsic Allergic Alveolitis resemble a viral or bacterial infection.[32] They include chills, fever, sweating, malaise, anorexia, nausea, headache, chest tightness, a non-productive cough and dyspnea without wheezing developing from 4 to 6 hours after exposure. The symptoms resolve spontaneously in 12 to 18 hours but will recur on reexposure. Farmer's lung and Bird fancier's lung are forms of extrinsic allergic alveolitis. There is a decrease in the forced vital capacity (FVC) and one second forced expired volume (FEV_1) of the lungs (See Appendix 1). Non atopic subjects usually exhibit this single stage response after short term exposure to the antigen to which they are sensitised. The reaction can be blocked by sodium cromoglycate but not by isoproterenol and can be improved by the use of corticosteroids.

A two stage reaction may be seen in atopic subjects. Immediately after exposure there is a typical asthmatic reaction (type 1) which is followed by a late type III reaction developing from 4 to 6 hours afterwards.

In some cases of a dual type response although the FEV_1 decreases there is little change in FVC indicating that the physiological changes in the late phase are primarily obstructive involving the larger airways.

3.3 Skin Allergy

When the skin reacts adversly to the working environment it can do so in a variety of ways[33]. Its commonest reaction is to become inflamed, a condition known as dermatitis or eczema. Inflamed skin looks red, swollen, blistered, weeping, flaky or cracked. It usually itches.

The commonest causes of occupational dermatitis are chemical substances in contact with the surface of the skin. This contact dermatitis may be caused by direct physical damage through irritation ie. acids, alkalis and organic solvents. It may also be caused by sensitisation involving an allergic mechanism when the substance involved is referred to as a contact allergen or contact sensitiser. Many contact sensitisers do not feel harmful to the skin and their effect may take months or years to show. Dermatitis may also be caused by a phototoxic or photoallergic mechanism where the additional stimulus of sunlight or UV light is required in conjunction with the chemical agent.

Urticaria (blistering of the skin commonly seen in allergy to ivy or nettles) may also occur in occupational environments and be caused by allergic as well as non-allergic mechanisms.

Adverse reactions to ingested materials (eg. food allergies) are commonly manifest by way of urticarial responses.

Other skin reactions occur to particular chemicals found in the working environment eg. oil acne which looks similar to teenage spots but is caused by excessive exposure to mineral oil.(eg in machine workers in the engineering industry)

3.4 Allergy and the eye

The skin of the eyelids is susceptible to the same types of hypersensitivity disorders and infections which involve the skin of other parts of the body.[34] Erythematous and exudative lesions may occur with scaling and crusting in later stages.

The other principal site in the eye involved in adverse reactions is the conjunctiva (the membrane covering the front of the eye). Contact sensitisation may produce conjunctivitis (inflammation of the conjunctiva) characterised by a papillary response, pronounced vasodilation, oedema and watery discharge. Conjunctivitis is the chief ocular manifestation of many allergies to common airborne substances and is often seen in hay fever. A milky appearance and stringy exudate are characteristic of an allergic conjunctivitis in contrast to the brilliant red appearance and purulent exudate found with bacterial conjunctivitis.

Allergen in direct contact with the conjunctiva interacts with IgE bound to mast cells initiating the release of mediators (including histamine, slow reacting substance of anaphylaxis SRS-A, and phagocyte activating factor PAF) which affect local blood vessels, smooth muscle and secretory glands and give rise to the clinical manifestations observed.

3.5 Properties of Allergens

With regard to respiratory allergies several factors predispose individuals to sensitisation by a particular agent: The nature of the organic dust or gas, the degree of exposure, the immunologic status of the patient[17] and whether they are smokers.[37-40]

The physical and chemical properties of a particulate or gaseous antigen determine its immunogenicity. The size of the particle determines whether it reaches the bronchioles and alveoli where reaction occurs.[35] Gases and volatile liquids will travel further than large particles. The solubility of the particle dictates whether it is absorbed by the lymphatics and blood vessels or phagocytosed by alveolar macrophages.

The intensity and duration of exposure are important aspects influencing the occurrence and the mode of presentation of the disease. A certain degree of exposure over a given time may give rise to tolerance in some individuals. Exposure at a high intensity is likely to precipitate irritant phenomena in most individuals which will probably mask

allergic effects even when exposure is reduced.

Differences in the immunologic status of patients clearly influences their likelihood of being sensitised. The reason for only a few individuals in a particular group of exposed workers becoming sensitised to a given agent is not understood. The reactivity of the individual is clearly different and this may stem from a variety of reasons including genetic factors. The concept of atopy[18;36] is part of this. Evidence suggests that most workers exposed to a particular chemical are likely to develop antibodies to it without becoming sensitised. The elicitation of a type III response to a particular antigen by some individuals in contrast to others developing a type I or dual response further illustrates this difference.

3.6 Sources of Occupational Allergens

Even in occupational environments sensitising agents arise from animal or vegetable sources (including micro-organisms) or from non-living (industrial) chemicals. (see table 4.) In the case of living or dead animal matter and with fungi and bacteria the allergens are generally proteins (including

TABLE 4 : OCCUPATIONAL ALLERGENS

SUBSTANCES REPORTED AS GIVING RISE TO CASES OF SENSITISATION TO WORKERS IN VARIOUS OCCUPATIONAL ENVIRONMENTS.

ANIMAL SOURCES

Animal dander - hair, epidermal squamae, urine, faeces [42-49]

Arthropods [50-62]

VEGETABLE SOURCES

Flour dust [63-66]

Cotton seed [67;68]

Castor bean [69;70]

Grain dust [62;71]

Garlic [72-74]

Gums [75]

Soybean dust [76]

Western Red Cedar wood dust [77-84]

Other wood dusts [85-92]

Colophony resin [93-100]

Papain [101-103]

Coffee bean [104-106]

Henna [107;108]

Mushrooms [109]

Bromelain (from pineapple) [110-111]

Flax seed [112;113]

Hemp [112;113]

Maiko [113]

TABLE 4 CONTINUED : OCCUPATIONAL ALLERGENS

MICRO-ORGANISM SOURCES

Spores of thermophyllic and other actinomycetes [114; 115 - 118]

Spores of other fungi — especially Aspergillus spp. [119 - 124]

Enzymes of Bacillus subtilis (used in detergents) [8; 125 - 131]

Antibiotics derived from Penicillium spp. [132 - 133]

NON-LIVING (INDUSTRIAL) SOURCES

Platinum salts [21; 134 - 138]

Chromate salts [139]

Nickel salts [140]

Phenyl mercuric compounds [141]

Synthetic fibres [142]

Persulphate salts [108]

Epoxy resin systems [37; 143 - 153]

Isocyanates [154 - 171]

Acrylates [172 - 175]

Reactive dyes [176 - 179, 333]

Other reactive organic chemicals (See Tables 5 to 9)

enzymes) or macromolecules. Inorganic (mineral) or simple organic chemicals found in industrial or other occupational environments are increasingly being implicated as sensitising reagents.

Ultimately the chemical nature of the agents is important rather than its source. The causal agents of allergic reactions due to wood dust and pine resins have been identified as simple organic chemicals.[41] Obviously in the case of animal matter, micro-organisms, spores etc. several proteins and other chemicals intimately combined may be involved as the causal agent making extraction and identification of individual chemicals extremely difficult.

3.7 Diagnosis of Occupational Allergy

Identifying the causal agent and establishing the aetiology of a disease may be difficult but defining its pathogen sis (ie. the actual development of the disease) can be very involved and apparentlyimpossible yet this must be achieved in order to promote successful treatment of patients and in prevention of further cases of the disease.

To ascertain a proper diagnosis of a disease involves not only detailed questioning and clinical examination of the patient but also appropriate physical testing (lung function, bronchial provocation and skin tests) and immunological investigations. (Appendix I summarises test procedures.)

Bronchial provocation tests in asthma and allergic alveolitis are a pragmatic means of aetiologic diagnosis that, at the same time, reproduce some or all of the clinical manifestations. In this respect the test reactions provide models of the clinical disorder and are useful in trying to interpret the variable history, in particular of clinical asthma.

By delivering controlled amounts of the suspected offending material either by aerosol nebuliser and face mask or by inhalation of vapour in a closed environment, or as a dust diluted in lactose powder, one can repeatedly determine respiratory function and obtain valuable information about patterns of bronchial reactivity as well as the effect of therapeutic agents. Unfortunately bronchoprovocation challenge testing affords little useful information concerning underlying immunological or non-immunological mechanisms.

The use of various treatment drugs in connection with provocation challenge testing provides some additional information as to the aetiology and pathogenesis of a particular disease.

Experimental, challenge-induced, immediate asthma readily responds to treatment with beta adrenergic stimulants such as iso-proterenol but not to inhaled or systemic corticosteroids[180]. On the other hand, late asthmatic reactions due to occupational agents characterised by an interval of one to two hours between exposure and onset of

respiratory symptoms and prolonged asthmatic response can be inhibited by corticosteroids such as beclomethasone dipropionate[181]. These late reactions also respond partially but poorly to beta-adrenergic stimulants. In other cases when dual, early and late asthmatic reactions occur both the immediate and late components can be prevented by prior administration of sodium cromoglycate some minutes before bronchial challenge[182]. This drug, which was originally shown to protect a sensitised subject against an asthmatic reaction induced by the inhalation of house dust extract appears to inhibit the release of pharmacological mediators in man but apparently does not prevent antigen-antibody interaction.

3.8 Common Occupational Allergens and Their Effects

The following paragraphs in this section summarise the observed effects of some of the organic chemicals which are common occupational allergens and of the substances containing them. More detailed information on the effects of particular chemicals identified as causal allergens is contained in Tables 5 to 9 arranged according to the structure of the molecule concerned.

Allergic responses to epoxy resin or its constituents have been widely reported. Epoxy resin systems are amongst the most important causes of industrial contact dermatitis. The uncured resin is the commonest cause but curing agents and even the cured resin may cause dermatitis[146;149;151;183-187]. Cases of adverse respiratory symptoms have also been documented[37;144;145;147;148;150;152;153].

Epoxy resin systems have two basic components, the uncured resin and a curing agent or hardener. The resins vary in composition but all are long chain polymers commonly produced as condensation products of epichlorohydrin and bisphenol A and they vary from low viscosity liquids to solids depending on molecular weight. The resins are relatively stable in themselves but contain terminal reactive epoxy groups and side chain hydroxyl groups. The resins are converted to hard solids by the addition of a curing agent or hardener. In some systems external heat is necessary and these commonly use acid anhydrides as curing agents while others are cold curing, notably those using amine compounds. In either case curing of the resin is brought about by chemical splitting of the epoxy ring leading to cross linkages between the long chain resin molecules producing macromolecular three dimensional structures. During the curing process fumes of resin and curing agents are emitted.

It seems likely that the pulmonary hypersensitivity reactions result from the presence of curing agents such as polyamines (diethylenetriamine, triethylenetetramine, piperazine) or acid anhydrides (phthalic anhydride) rather than the polymer itself.[37]

The sensitisation by anhydrides is discussed in detail in Chapter 5.

Investigations of the allergenicity of epoxy resins and the sensitising capacity of their constituents using guinea pigs has shown[188-192] that epoxy resins of low molecular weight (340 daltons) is a potent sensitiser in these animals and that the sensitising capacity decreases in inverse proportion to the increase in average molecular weight of the resin mixtures.

Isocyanates are widely used in industry for the production of several products including polyurethane foams and are known to have toxic effects. They are mild skin irritants and sensitisation of the skin can occur.[193-195] In sufficiently high concentrations isocyanates have a primarily irritant effect on the respiratory tract causing dry throat and coughing.[196-198] Asthmatic attacks may result and may occur immediately on exposure or some hours later,[199-201] Some workers (about 5% of exposed persons) may become sensitised.

The two most common compounds are toluene di-isocyanate (TDI) and diphenyl methane di-isocyanate (MDI). Immediate, non-immediate and dual reactions to TDI have been observed and it has been shown[171;202;204-206] to induce recurrent nocturnal asthma.

The use of ultra violet cured inks has given rise to allergic reactions in exposed workers.[179;207-217] The ink usually consists of one or more conventional pigments dispersed in a polymeric vehicle. Included in this vehicle are polyfunctional acrylate monomers such as trimethylol propane triacrylate (TMPTA), pentaerythritol triacrylate

(PETA) and hexanediol diacrylate alone or in combination with monofunctional acrylic monomers such as hydroxyethyl acrylate or 2 - ethyl hexyl acrylate. Other constituents include UV reactive unsaturated polymers (often also acrylated materials), photoinitiators (eg. benzophenone), diluents (alcohols or phthalates), hydrogen transfer agents (eg. triethanolamine) and miscellaneous additives (including stabilisers, surfactants etc.) The UV radiation is absorbed by the photoinitiators resulting in the generation of free radicals which in turn cause polymerisation of the resin in which the pigments are incorporated and thus cures the ink film.

TMPA and PETA are known to be strong allergens and cross reactivity between them and other acrylates has been demonstrated.[219] The principal symptom is an erythematous pruritic rash and since its distribution on affected workers generally includes the face and neck as well as the hands and arms, it is suggested that airborne materials play an important role in eliciting the reaction.

Allergic contact sensitisation to several monofunctional acrylic monomers has also been widely reported,[215-222;417] with methyl methacrylate most frequently incriminated although acrylonitrile acrylamide, ethyl hexyl acrylate and N tert butyl maleamic acid have been cited.

Resins used in the Letterflex printing process, which also uses UV light to trigger polymerisation, are reported as allergens.[223-226]

However a polythiol (commonly pentaerythritol tetrakis 3 mercapto propionate) seems to be the chemical responsible. Two types of symptoms are known :-

i) Skin lesions - some of an irritant pruriginous and erythematous nature appearing on uncovered parts of the body; others of an eczematous nature primarily affecting the hands.

ii) General symptoms including various degrees of conjunctivitis and respiratory disturbances with sneezing and rhinorrhea or conversely, nasal obstruction, coughing, dyspnea, and true asthmatic attack.

Amines present in the rubber of tyres have been reported[227-233] to cause allergic contact dermatitis in exposed workers. N-isopropyl-N phenyl paraphenylene diamine (IPPD) and related compounds in particular give rise to eczema characterised by distinctly vesicular lesions on the backs of hands and forearms. Some cross reactivity occurs.

Occupational asthma due to sensitivity to colophony fumes have been reported[93-100]. Colophony, which has been used as a soldering flux since ancient times, is the residue left after turpentine has been distilled from pine resin. It consists largely of abietic and pimaric type resin acids, the exact composition depending on the source of the material.

The common symptoms are wheezing, breathlessness and cough; sputum, rhinitis and eye irritation have also been observed. The wheeze and breathlessness generally persist after work in the evening. Bronchial provocation testing in sensitised workers[95] generally elicits both immediate and late asthmatic reactions. Colophony itself is also a potent skin sensitiser.[234-236;411;412]

Asthma due to inhalation of wood dusts is generally[87;237] an irritant phenomenon. However, asthma caused by occupational exposure to dust from Western Red Cedar has been reported[77-84] and appears to be a respiratory allergy. The syndrome includes chest tightness, dry irritating cough and wheeze (becoming worse at the end of the day) followed by nocturnal cough and wheezing. Nocturnal symptoms often persist for several days after cessation of exposure.[414] A type 1 reaction is thought to be involved and the principle allergen (hapten) has been identified[41] as plicatic acid.

Cases of other wood dusts acting as respiratory allergens have been reported[85-92] and many woods are known[87;88;238-243;413] to be contact sensitisers.

STRUCTURAL BASIS OF ACTIVITY

4.1 Functional Groups

Whilst physical factors (eg. particle size, solubility, volatility etc.), concentration and route of 'invasion' of the causal agent are important, structure and molecular configuration are the key factors which affect the elicitation of a particular response. Indeed, since all biological activities are primarily effected by chemical means, the interaction between molecules (or more precisely between functional groups present on the molecules) is an essential precursor of the observed response.

At the molecular level, chemical reactivity is determined by the presence of particular functional groups and their relative accessibility. The accessibility of a given functional group present on the molecule is a consequence of its three-dimensional structure which determines whether it is inhibited from exerting an appreciable affect by the location of other atoms or groups (steric hindrance) or remains free to react with other molecules. The greater the complexity of the molecule the more likely it is that certain groups will be prevented from acting. Conversely and more importantly in such molecules two or more functional groups are likely to be brought together on the surface of the molecule forming an 'active site'. this is

particularly relevant in the case of proteins and other macromolecular substances and indeed constitutes the very basis of enzyme action.

Clearly the chemical composition and structure ultimately determines the three-dimensional configuration of the molecule. With small molecules the active functional groups are easier to determine but when conjugates are formed (eg. between haptens and carrier proteins) the reactivity of the resulting complex will be influenced not only by the remaining accessible groups of the smaller molecule but also by the groups of the larger molecule in close proximity to it.

Key functional groups present on molecules of substances which have given rise to allergic and other adverse reactions in man (or experimental animals) include the carbonyl-, amino-, and amido- groups as well as the presence of unsaturated centres in certain molecules. Obviously the close proximity of other groups to these key groups, either linked chemically or simply by position, will modify the reactivity of the key group.

Tables 5 to 9 summarise the observed symptoms of adverse reactions in humans (and in animal studies) following occupational exposure to particular organic chemicals containing one or more of these key functional groups. Adverse reactions which have not been shown to involve sensitisation (either by direct immunological evidence or by implication following the usual criteria) have not

TABLES 5 TO 9

A SUMMARY OF THE OBSERVED REACTIONS TO, AND THE EFFECTS OF, SMALL MOLECULAR WEIGHT ORGANIC CHEMICALS PRESENT IN CERTAIN INDUSTRIAL AND RELATED WORKING ENVIRONMENTS.

Structural Formulae, Index number, Solubility and Physical Data from the Merck Index 10th Edition 1983.[244]

Long Term Exposure Limits (LTEL), Short Term Exposure Limits (STEL) from Guidance Note EH 40 (Health and Safety Executive).[245]

TABLE 5a ALDEHYDES

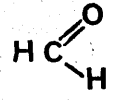
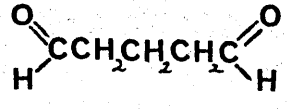
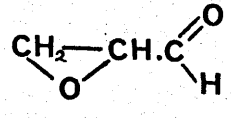
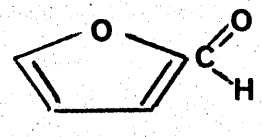
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
FORMALDEHYDE (4093 gas) (4095 soln.)		ASTHMA (late reaction) [246-256] EXTRINSIC ALLERGIC ALVEOLITIS [257] DERMATITIS [258-279]	STEL & LTEL 2ppm; 3mg/m^3 widely used: disinfectant, preservative, formaldehyde resins, tanning agent, dye improver, photographic processing, paper making
GLUTARALDEHYDE b.pt 187°		DERMATITIS [280-286]	STEL & LTEL 0.2ppm; 0.7mg/m^3 antiperspirant, sterilising fluid, tanning agent capable of cross linking proteins and thereby forming new antigenic site by this mechanism
GLYCIDALDEHYDE (2,3 epoxypropinal)		DERMATITIS [287]	skin irritant reacts with primary amino groups of proteins
FURFURAL (4155) b.pt 161.8° colourless oily liquid volatile in steam soluble in water		ASTHMA (late reaction) [288] DERMATITIS [287]	STEL 15ppm; 60mg/m^3 LTEL 5ppm; 20mg/m^3 used in the manufacture of furan resins

TABLE 5a (continued) ALDEHYDES

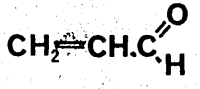
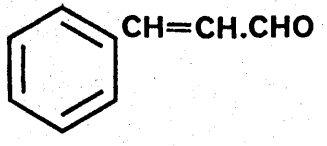
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
ACROLEIN (123) (acrylic aldehyde) b.pt 52.5° unstable - polymerises		ASTHMA [244] (high concentration causes pulmonary oedema) DERMATITIS [287]	LTEL 0.1ppm; 0.25mg/m^3 STEL 0.3ppm; 0.8mg/m^3 irritant to eyes and mucosa vapours cause lacrimation
CINNAMALDEHYDE b.pt 246° slightly soluble in water		DERMATITIS [289-291]	found in cinnamon readily reacts with amines

TABLE 5b QUINONES

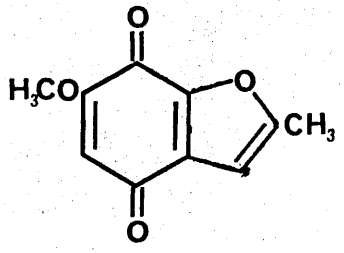
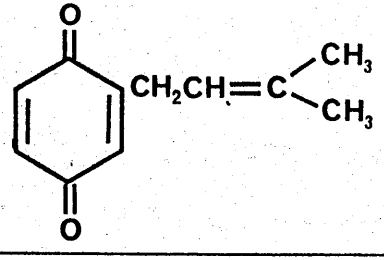
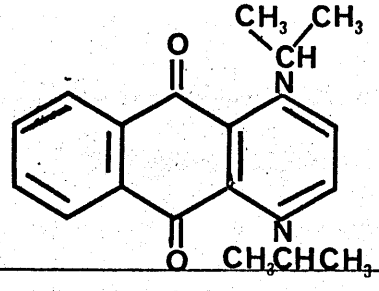
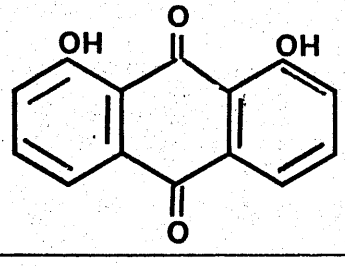
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
6-METHOXY-2METHYL-3,5 DIHYDRO BENZO (b) FURANO 4,7 DIONE		DERMATITIS [292]	present in Australian blackwood
2-DIMETHYL ALLYL 1,4 BENZOQUINONE		DERMATITIS [293]	
1,4 BIS (ISOPROPYL AMINO) ANTHRAQUINONE		DERMATITIS [294]	present in felt tip pen ink
1,8 DIHYDROXY ANTHRAQUINONE (Danthron) (2802) m.pt 193-197° sublimes orange needles almost insoluble in water		DERMATITIS (photocontact) [295]	dye

TABLE 5b (continued) QUINONES

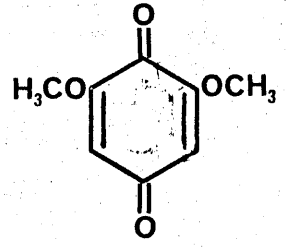
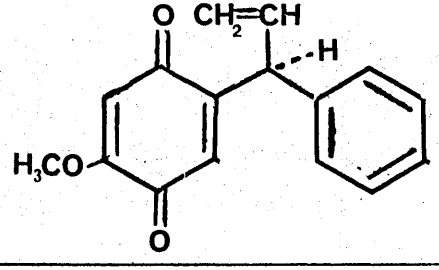
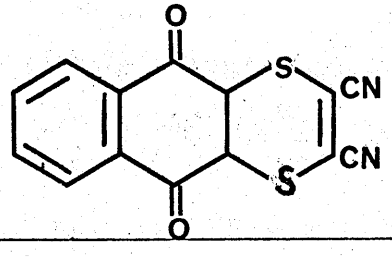
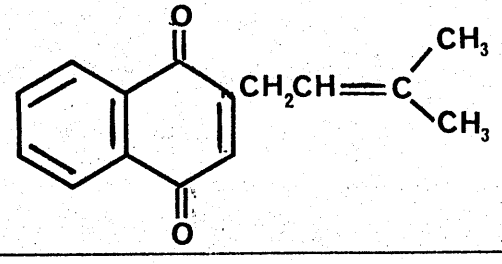
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
2,6-DIMETHOXY-1,4-BENZOQUINONE (3212) golden yellow prisms m.pt 256 sublimes volatile with steam		DERMATITIS [292]	present in Australian blackwood
R-4 METHOXY DALBERG IONE		DERMATITIS [238;241;242]	allergen in rosewood
DITHIANONE (5,10-Dihydro-5,10-dioxonaptho(2,3,6)-1,4 dithin 2,3 dicarbo nitrile)		DERMATITIS [238;239]	present in henna
DESOXYLAPACHOL		DERMATITIS [238;240]	principle sensitiser in teak wood also an irritant

TABLE 5b (continued) QUINONES

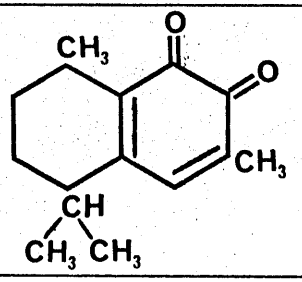
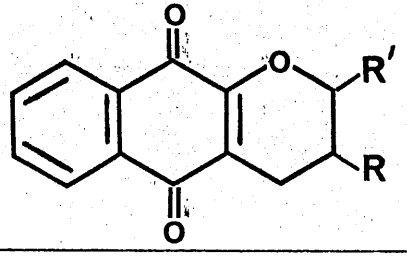
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
MANSONONE A		DERMATITIS [238]	present in Mansonia wood also an irritant
NAPTHO FURANO QUINONES		DERMATITIS [88]	allergen present in wood of peroba do campos

TABLE 5c CARBOXYLIC ACIDS

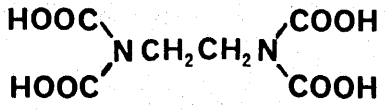
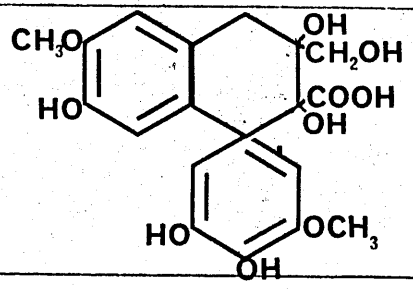
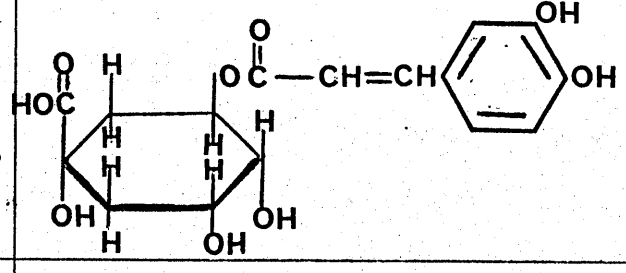
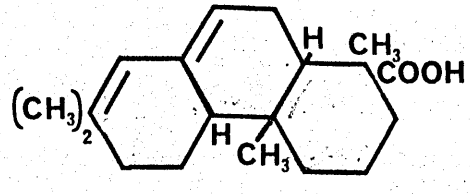
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
ETHYLENE DIAMINE TETRA ACETATE (3476) (Edetic acid or EDTA) soluble in water at 25°		DERMATITIS [297-299]	chelates metals, could react in chemical configuration of protein which carries ions especially metal cations used in the cosmetic industry
PLICATIC ACID		ASTHMA (immediate, late and dual reactions) [77; 79-83] RHINITIS [77; 82]	active principle in Western Red Cedar wood complement involved in the allergic reaction [300] may react as a phenol compound
CHLOROGENIC ACID (2121) hemihydrate needles from water m.pt 208° soluble in water		ASTHMA [104-106; 301]	active principle in green coffee bean may react as a phenol compound
ABIETIC ACID (1) monoclinic plates m.pt 172-175° insoluble in water		ASTHMA (immediate type) [93-100] DERMATITIS [234-236]	one of the active principle in colophony pine resin used as solder, cosmetic, adhesive tapes, varnish etc commercial abietic made by heating rosin

TABLE 5c (continued) CARBOXYLIC ACIDS

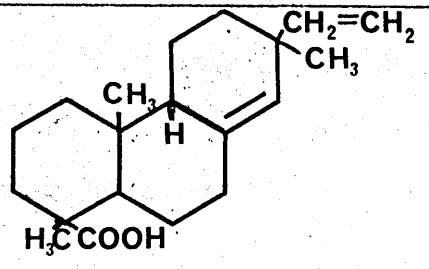
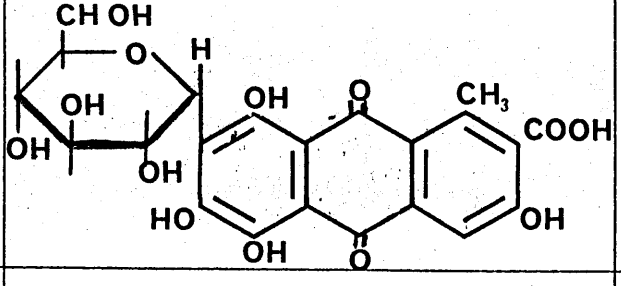
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
PIMARIC ACID		ASTHMA [93-100] DERMATITIS [234-236]	one of the active principles in colophony pine resin
CARMINIC ACID red prisms soluble in water		ASTHMA (dual reaction) [302] GASTRO INTESTINAL SYMPTOMS [302] ALLERGIC CHEILITIS [303] (when used as a lip salve)	Carmine- aluminium calcium lake insoluble in cold water or dilute acids. partially soluble in hot water dye (used in foods)

TABLE 5d ACYL HALIDES

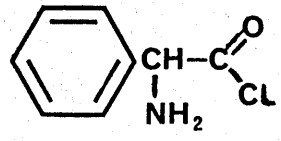
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
PHENYL GLYCINE ACID CHLORIDE		ASTHMA (immediate type) [304]	also an irritant highly reactive - combines readily with proteins

TABLE 5a ACID ANHYDRIDES

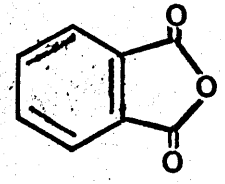
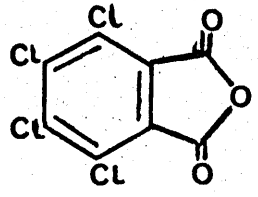
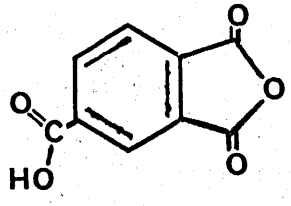
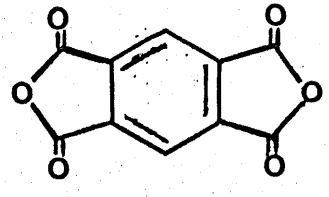
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
PHTHALIC ANHYDRIDE (7179) white lustrous needles m.pt 130.8° b.pt 295° sublimes soluble in water		ASTHMA (immediate and delayed reactions) [37; 305-309] RHINITIS [307]	LTEL 1ppm; 6mg/m^3 STEL 4ppm; 24mg/m^3 used as hardener in epoxy resin manufacture
TETRACHLOROPHTHALIC ANHYDRIDE		ASTHMA (immediate and late reactions) [310]	used as hardener in epoxy resin manufacture
TRIMELLITIC ANHYDRIDE (9370) crystals m.pt 161-163°		ASTHMA (immediate and late reactions) [311; 312] EXTRINSIC ALLERGIC ALVEOLITIS (LRSS) [312] RHINITIS [311] PULMONARY DISEASE ANAEMIA SYNDROME [313]	used as hardener in epoxy resin manufacture and in the manufacture of plasticisers LTEL 0·04 mg/m^3
PYROMELLITIC DIANHYDRIDE		ASTHMA (immediate type) [148]	used as epoxy adhesive hardener could act as cross-linking agent

TABLE 5f AMIDES

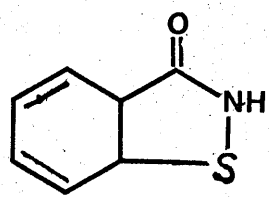
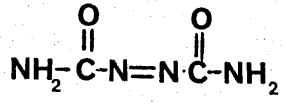
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
1,2-BENZISOTHIAZOLIN-3-ONE yellow needles m.pt 137.5°		DERMATITIS [314]	used as preservative in plastic emulsions
AZODICARBONAMIDE (919) orange red crystals m.pt 225° soluble in hot water		ASTHMA [315]	used as a blowing agent in plastics manufacturing & bleach agent in cereal flour

TABLE 6a ACRYLATES

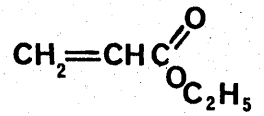
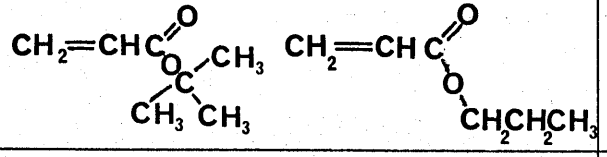
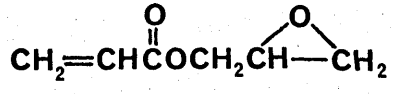
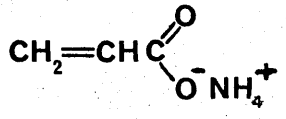
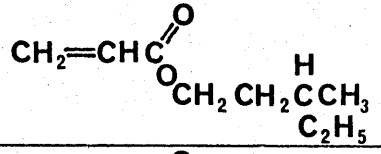
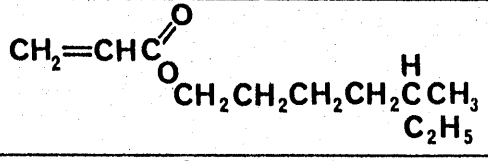
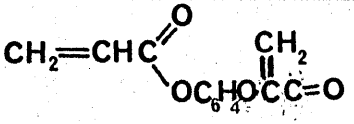
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
ETHYL ACRYLATE (3688) liquid f.pt -72° b.pt 99.4° polymerises on distillation		DERMATITIS [316]	LTEL 25ppm; 100mg/m^3
BUTYL ACRYLATE (1523) liquid b.pt 145° soluble in water		DERMATITIS [316]	LTEL 10ppm; 55mg/m^3
GLYCIDYL ACRYLATE		DERMATITIS [318]	
AMMONIUM ACRYLATE		ASTHMA [172] DERMATITIS [172]	
2-ETHYL BUTYL ACRYLATE b.pt 82°		DERMATITIS [219]	
2-ETHYL HEXYL ACRYLATE b.pt 130° insoluble in water		DERMATITIS [219]	
1,6 HEXANE DIOL DIACRYLATE		DERMATITIS [209;213;214]	

TABLE 6a (continued) ACRYLATES

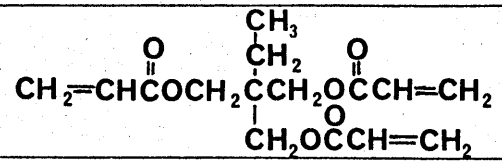
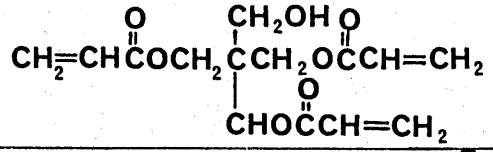
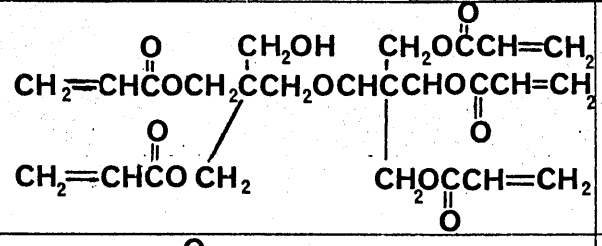
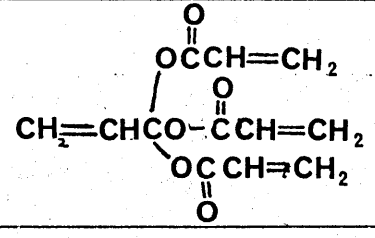
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
TRIMETHYLOL PROPANE TRIACRYLATE (TMPTA)		DERMATITIS [209-211; 213; 214; 308]	used in manufacture of UV cured inks animal studies [317]
PENTA ERYTHRITOL TRIACRYLATE (PETA)		DERMATITIS [209-211; 213; 214; 308]	used in manufacture of UV cured inks
DIPENTA ERYTHRITOL MONOHYDROXY PENTA ACRYLATE (DEMPTA)		DERMATITIS [210; 308]	used in manufacture of UV cured inks
TRIPROPYLENE GLYCOL TRIACRYLATE		DERMATITIS [211]	used in the manufacture of UV cured inks

TABLE 6b METHACRYLATES

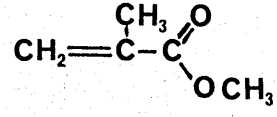
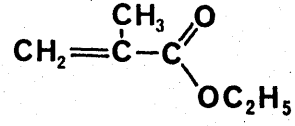
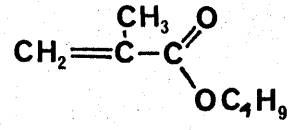
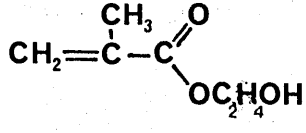
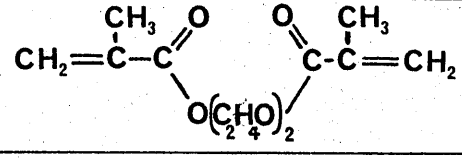
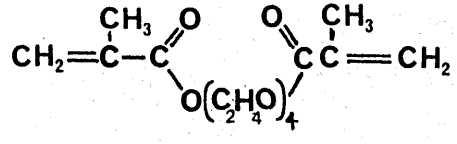
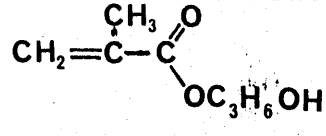
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
METHYL METHACRYLATE b.pt 101° slightly soluble in water		ASTHMA [173] DERMATITIS [221; 320]	LTEL 100ppm; 410mg/m^3 STEL 125ppm; 510mg/m^3 animal studies [321]
ETHYL METHACRYLATE b.pt 117° slightly soluble in water		DERMATITIS	animal studies [321]
N-BUTYL METHACRYLATE b.pt 160° insoluble in water		DERMATITIS	animal studies [321]
2-HYDROXYETHYL METHACRYLATE		DERMATITIS [322; 323]	
DIETHYLENEGLYCOL DIMETHACRYLATE		DERMATITIS [322; 323]	
TETRAETHYLENEGLYCOL DIMETHACRYLATE		DERMATITIS [322-324]	
1-HYDROXYPROPYL METHACRYLATE		DERMATITIS [219]	

TABLE 6c ACRYLAMIDES

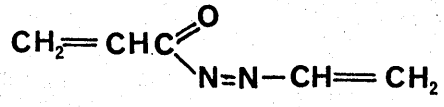
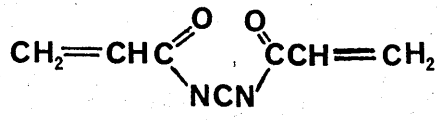
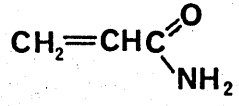
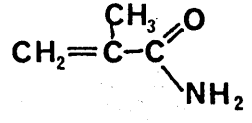
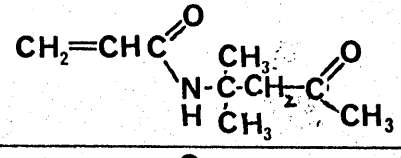
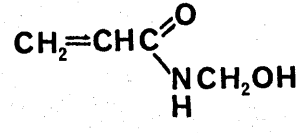
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
ACRYLONITRILACRYL AMIDE		DERMATITIS [319]	
N,N' METHYLENE BIS ACRYLAMIDE		DERMATITIS [325]	used in printing
ACRYLAMIDE (125) crystals m.pt 84.5° soluble, polymerises		DERMATITIS [322; 325]	LTEL 0.3 mg/m^3 STEL 0.6 mg/m^3
METHACRYLAMIDE		DERMATITIS [319]	
DIACETONE ACRYLAMIDE (2920) m.pt 57° white crystaline solid		DERMATITIS [319]	
N-METHYLOL ACRYLAMIDE		DERMATITIS [322;325;326]	

TABLE 6d ISOCYANATES

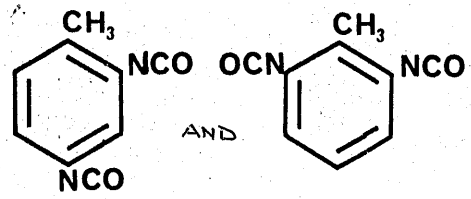
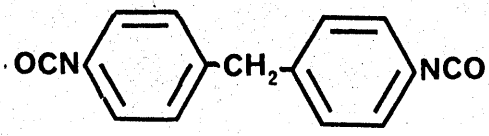
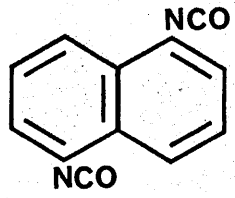
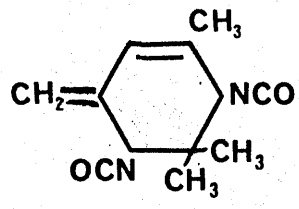
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
TOLUENE DIISOCYANATE (TDI) (9226) liquid m.pt 19.5-20.5° b.pt 251° polymerises reacts with water to give CO_2		[154;157;159-161;164;170;197;] ASTHMA (immediate, late and dual reactions) [199-201] EXTRINSIC ALLERGIC ALVEOLITIS [165;169]	LTEL 0·02 mg/m³ [CL] STEL 0·07 mg/m³ [CL] used in manufacture of flexible and rigid foams, synthetic rubbers and paint
DIPHENYL METHANE DIISOCYANATE (MDI)		[155;162-164;168;170;195;205] ASTHMA EXTRINSIC ALLERGIC ALVEOLITIS [165;168;204;205] DERMATITIS [193;195]	LTEL [CL] 0.02mg/m³ STEL [CL] 0.07mg/m³
1,5-NAPTHYLENE DIISOCYANATE		ASTHMA [167]	
ISOPHORONEDIISOCYANATE (IPDI)		ASTHMA [166;203]	LTEL [CL] 0.02mg/m³ STEL [CL] 0.07mg/m³

TABLE 6d (continued) ISOCYANATES

CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
HEXAMETHYLENE DIISOCYANATE	$OCNCH_2CH_2CH_2CH_2CH_2CH_2NCO$	ASTHMA [166;170]	LTEL 0·02 mg/m³ [CL] STEL 0.07 mg/m³ [CL]

TABLE 6a REACTIVE DYES

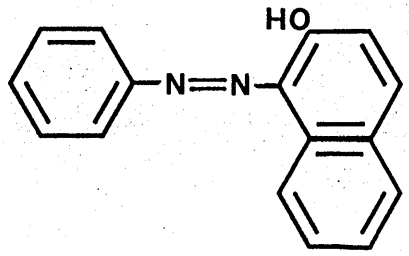
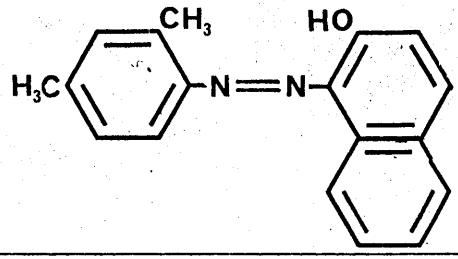
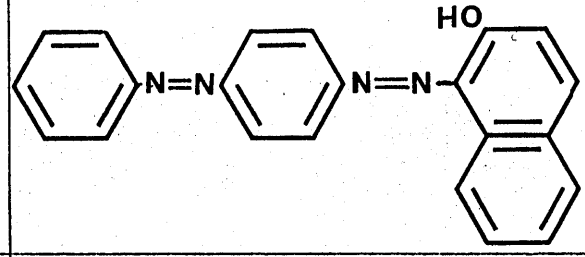
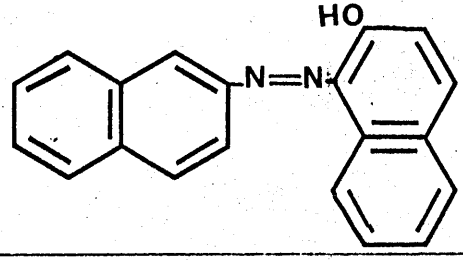
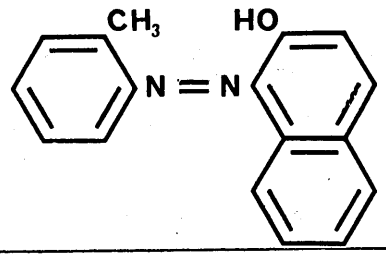
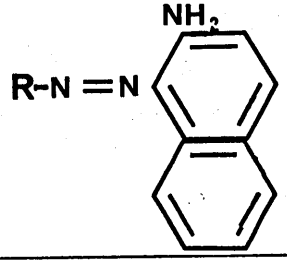
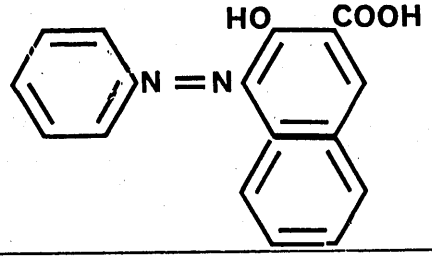
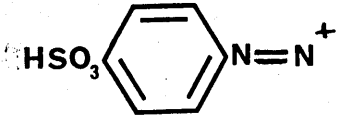
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
SUDAN I		DERMATITIS [331]	
SUDAN II		DERMATITIS [331]	
SUDAN III		DERMATITIS [331]	
VACANCEINE RED		DERMATITIS [331]	

TABLE 6a (continued) REACTIVE DYES

CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
ORANGE SS		PIGMENTED CONTACT DERMATITIS [331]	
YELLOW OB		PIGMENTED CONTACT DERMATITIS [331]	
BRILLIANT LAKE RED R		PIGMENTED CONTACT DERMATITIS [331;332]	
DIAZOBENZENE SULPHONIC ACID		EXTRINSIC ALLERGIC ALVEOLITIS [334] ASTHMA [176;335]	

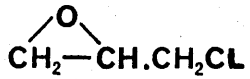
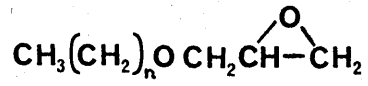
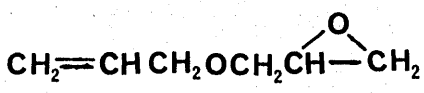
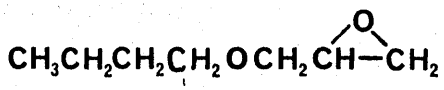
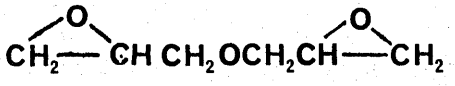
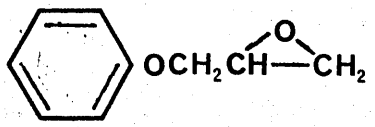
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
EPICHLORHYDRIN (3536) liquid m.pt-25.6° b.pt 117.9°insoluble		listed [287] as strong respiratory sensitiser but sensitisation not confirmed	LTEL 2ppm; 8 mg/m^3 STEL 5ppm; 20mg/m^3
EPOXIDE 7		DERMATITIS [336]	
ALLYL GLYCIDYL ETHER		DERMATITIS [287]	LTEL 5ppm; 22mg/m^3 STEL 10ppm; 44mg/m^3
n BUTYL GLYCIDYL ETHER		DERMATITIS [287]	LTEL 50 ppm; 270mg/m^3
DIGLYCIDYL ETHER		DERMATITIS [287]	LTEL & STEL 0·5ppm; 3mg/m^3
PHENYL GLYCIDYL ETHER		DERMATITIS [287]	
SEE ALSO :- GLYCIDYL ALDEHYDE GLYCIDYL ACRYLATE	TABLE 5a PAGE 49 TABLE 6a PAGE 59		

TABLE 7a EPOXIDES

TABLE 7b IMINES

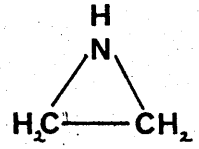
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
ETHYLENE IMINE (3748) liquid, polymerises easily. b.pt 56-57° miscible with water		DERMATITIS [287;337]	LTEL 0.5ppm; 1mg/m^3 widely used in many industries including polymer manufacturing

TABLE 8 AMINES

CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
ETHYLENE DIAMINE (3731) liquid b.pt 116° m.pt 8.5° soluble volatile with steam	$H_2NCH_2CH_2NH_2$	ASTHMA (late reaction) [338;339;341] DERMATITIS [342-347]	LTEL 10ppm; 25mg/m^3 irritant vapour used as solvent for shellac in developing photographs in preparation of dyes etc.
HYDRAZINE (4653) liquid b.pt 120.3° solvent, miscible with water	H_2NNH_2	DERMATITIS [348]	LTEL 0.1ppm; 0.1mg/m^3
DIETHYL TETRAMINE		DERMATITIS [341]	
DIETHYLENE TRIAMINE	$H_2NCH_2CH_2$ NH $H_2NCH_2CH_2$	ASTHMA [350] DERMATITIS	LTEL 1ppm; 4mg/m^3
TRIETHYLENE TETRAMINE	$H_2NCH_2CH_2\overset{H}{N}CH_2CH_2\overset{H}{N}CH_2CH_2NH_2$	ASTHMA [37;351] DERMATITIS [151;341]	
ETHANOLAMINE (3654) viscous hygroscopic liquid b.pt 170.8° strong base miscible	$HOCH_2CH_2NH_2$	ASTHMA [339]	LTEL 3ppm; 8mg/m^3 STEL 6ppm; 15mg/m^3 no obvious cause for allergic reaction
DIMETHYL ETHANOLAMINE	$HOCH_2CH_2N\begin{matrix}CH_3\\CH_3\end{matrix}$	ASTHMA (dual response) [360] RHINITIS [360]	no obvious cause for allergic reaction may be impurities

TABLE 8 (continued) AMINES

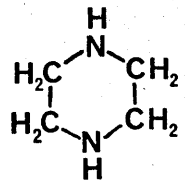
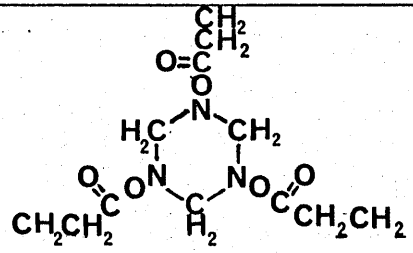
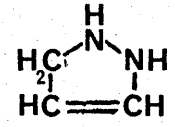
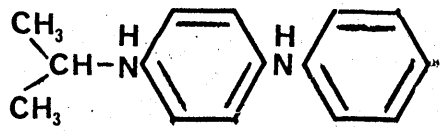
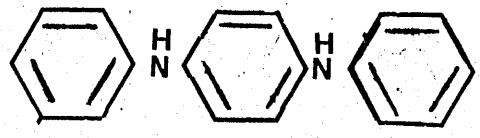
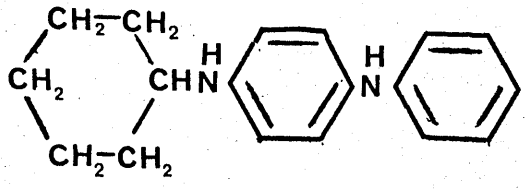
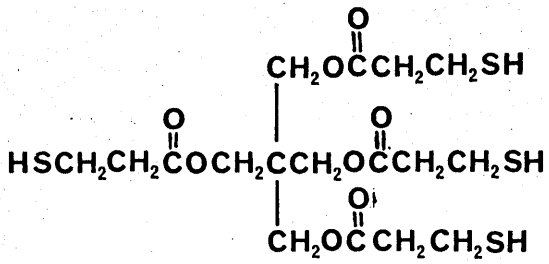
CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
AMINOETHYL ETHANOLAMINE	$HOCH_2CH_2\overset{H}{N}CH_2CH_2NH_2$	ASTHMA [361;362]	no obvious cause for allergic reaction may be impurities
CHLORAMINE T (2038) trihydrate prism fairly soluble in water	$CH_3C_6H_4SO_2NNaCl$	ASTHMA [363;364] (immediate and late reactions) DERMATITIS [363;365;366]	oxidising agent - can oxidise proteins
PIPERAZINE (7254) leaflets from alcohol m.pt 106° b.pt 146° strong base, absorbs CO_2 & H_2O from air		ASTHMA (late reaction) [352-354] DERMATITIS (immediate type wheal) [355-357]	
HEXAHYDRO 1,3,5-TRIACRYLOL S TRIAZINE		DERMATITIS [318]	may cross link protein
PYRAZOLINE (7745) liquid b.pt 144° volatile with steam miscible with water		DERMATITIS (pigmented) [359]	metabolites may be important

TABLE 8 (continued) AMINES

CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
p-PHENYLENE DIAMINE (1,4 diaminobenzene) (7089) white/red crystal m.pt 145-147° b.pt 267° soluble in water		ASTHMA [252;287;339] DERMATITIS [344]	LTEL 0.1mg/m^3 solvent in paint making accelerator in rubber production, used in fur industry may oxidise to quinone
ISOPROPYL PHENYL PARAPHENYLENE DIAMINE (IPPD)		DERMATITIS [227-233]	used in rubber manufacture
N,N'-DIPHENYL-p-PHENYLENE DIAMINE (DPPD) (3342) colourless leaflets m.pt 150 insoluble in water		DERMATITIS [228]	used in rubber manufacture
N-PHENYL-N'-CYCLOHEXYL-p-PHENYLENE DIAMINE (CPPD)		DERMATITIS [228]	used in rubber manufacture

CHEMICAL	FORMULA	SYMPTOMS (WITH REFERENCES)	REMARKS
PENTAERYTHRITOL TETRAKIS 3-MERCAPTOPROPIONATE		DERMATITIS [223;225] RHINITIS [223]	asthma also reported but not clearly established as allergic

been included. Reports of allergic contact dermatitis to related chemicals have been included for comparison purposes.

4.2 Bonding to protein

Strength or stability of bonds between a carrier molecule and a small hapten plays a critical role in the determination of its biological properties. Since haptens have to form stable complexes with carrier proteins in order to react with the immune system it has long been accepted that covalent binding of these units is necessary.[368,369] Weaker bonds (ionic or dipole including hydrogen bonding) can serve only when multiple bonds provide the necessary cumulative energy to the complex.

Carbonyl, amino and similar groups on haptenic molecules are therefore prime candidates for this task. Reactive anhydrides, quinones and acid chlorides have been shown to form hapten-protein conjugates by linking of their constituent carbonyl groups with amino groups of amino acid residues of protein. Similarly the isocyanate group of the various reactive aliphatic and aromatic isocyanates known to induce allergic reactions, is thought to be responsible for covalent attachment to protein.[38] TDI is capable of combining with $-NH_2$,-OH,-SH and -COOH groups[370] as well as undergoing self polymerisation and still retaining reactive isocyanate groups.[371] In the case of reactive dyes[10] covalent bonding between heterocyclic

halogen groups on the molecule and amino or hydroxyl functions of protein side chains can occur.[10] Indeed this type of linkage is used in the dyeing process.

The reactive side chains of amino acid residues commonly present in proteins and likely to be involved in protein binding to haptens are shown in table 10. The structures of probable haptens formed by several classes of reactive organic compounds with protein (linked via side chain groupings) are shown in figure 7.

The presence of unsaturated bonds in haptenic molecules does not seem to influence protein binding. In the case of abietic acid and pimaric acid (found in colophony resin) the unsaturated double bonds of these acids seem to be less important for protein binding than the carbonyl groups.[95] Similar evidence[156] has also been found in the case of TDI.

4.3 Conjugates

Molecules with more than one functional group capable of binding to protein may give rise to several different conjugates. Even with a given protein a molecule with two or more of the same functional groups may form two or more conjugates of separate structure. The position is further complicated in the case of molecules having different functional groups. With plicatic acid (found in Western Red Cedar) for example, carbonyl groups on the molecule could bind with lysine or arginine residues on a given protein to form a complex whilst alternatively

TABLE 10.

REACTIVE AMINO ACID SIDE CHAINS OF PROTEINS AVAILABLE FOR BINDING TO REACTIVE ORGANIC MOLECULES

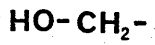
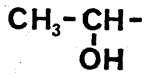
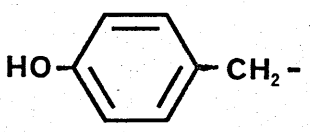
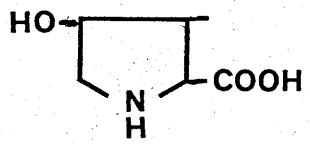
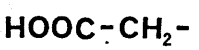
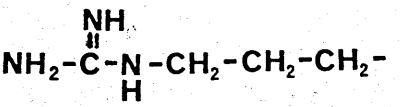
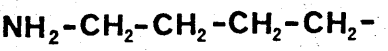
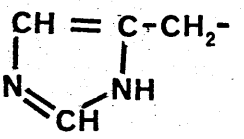
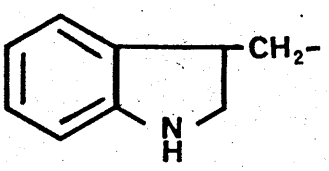
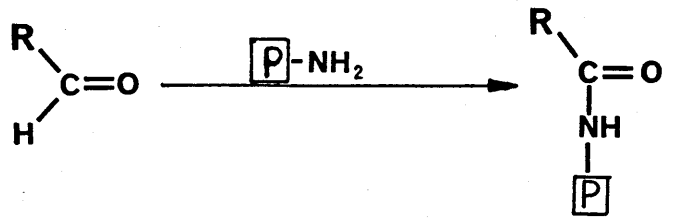
SERINE	
THREONINE	
TYROSINE	
HYDROXYPROLINE	
ASPARTIC ACID	
GLUTAMIC ACID	
ARGININE	
LYSINE	
HISTIDINE	
TRYPTOPHAN	

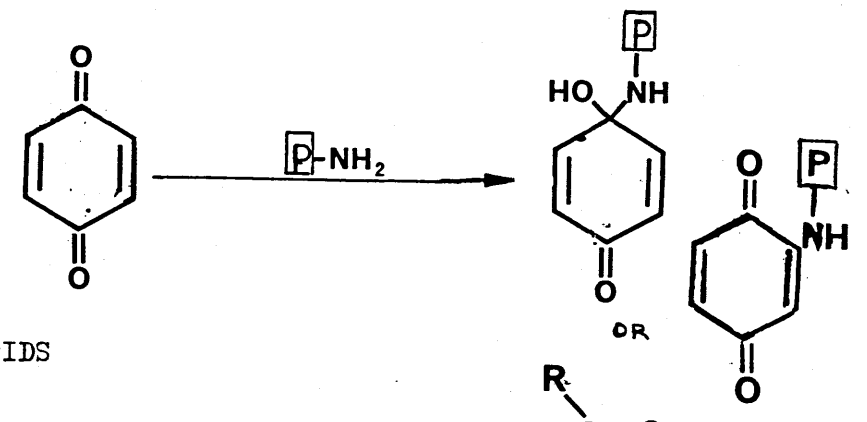
FIGURE 7.

STRUCTURES OF PROBABLE HAPTENS RESULTING FROM THE REACTIONS OF SIMPLE ORGANIC CHEMICALS WITH PROTEIN. (P)

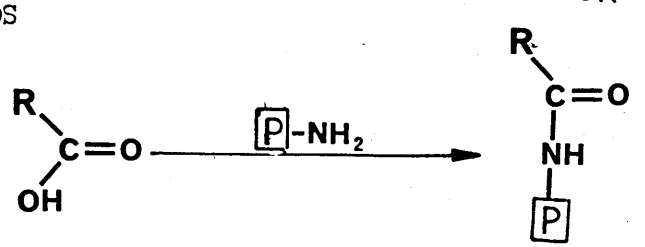
ALDEHYDES



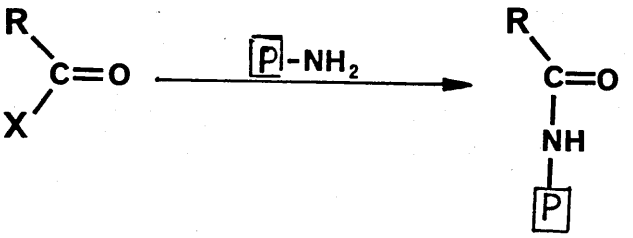
QUINONES



CARBOXYLIC ACIDS



ACYL HALIDES



ACID ANHYDRIDES

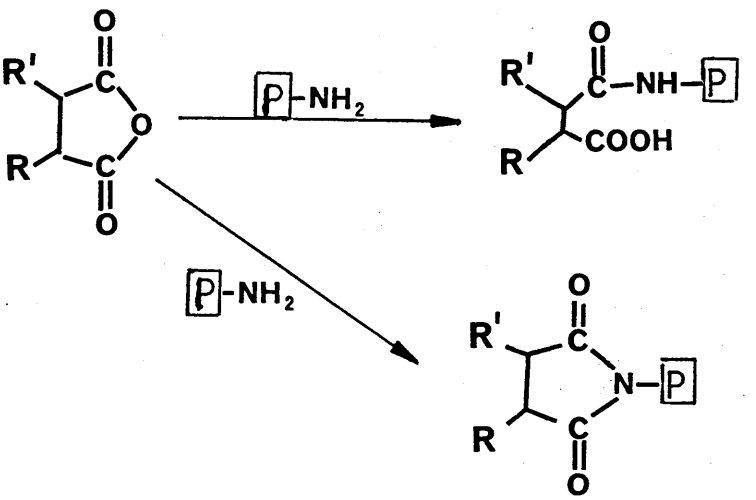
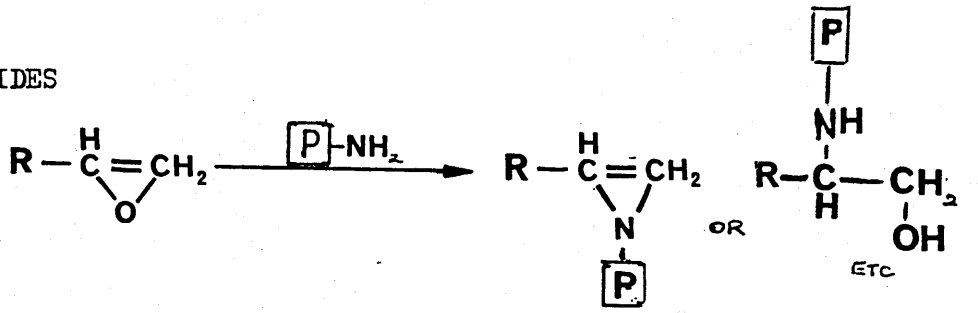


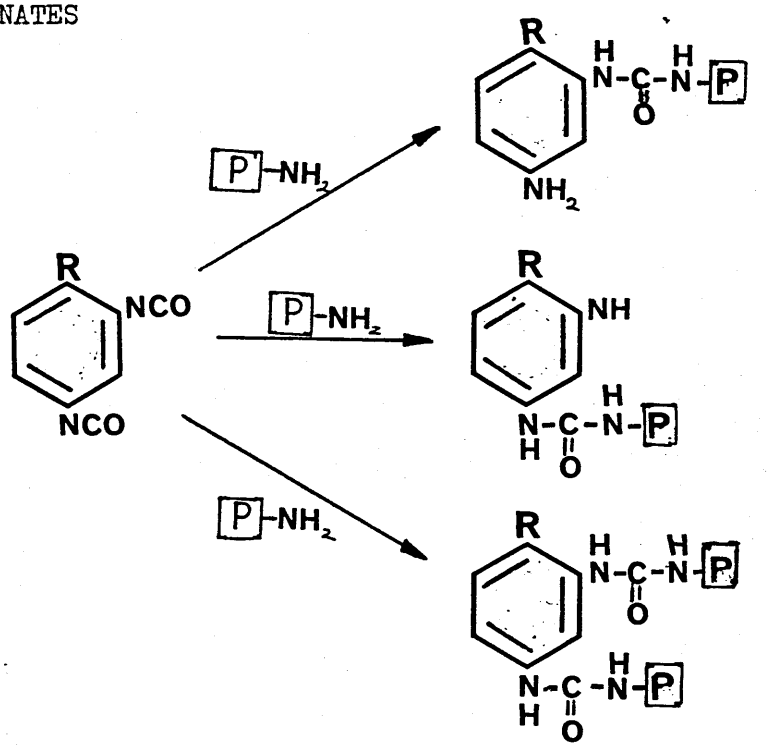
FIGURE 7. (continued)

STRUCTURES OF PROBABLE HAPTENS

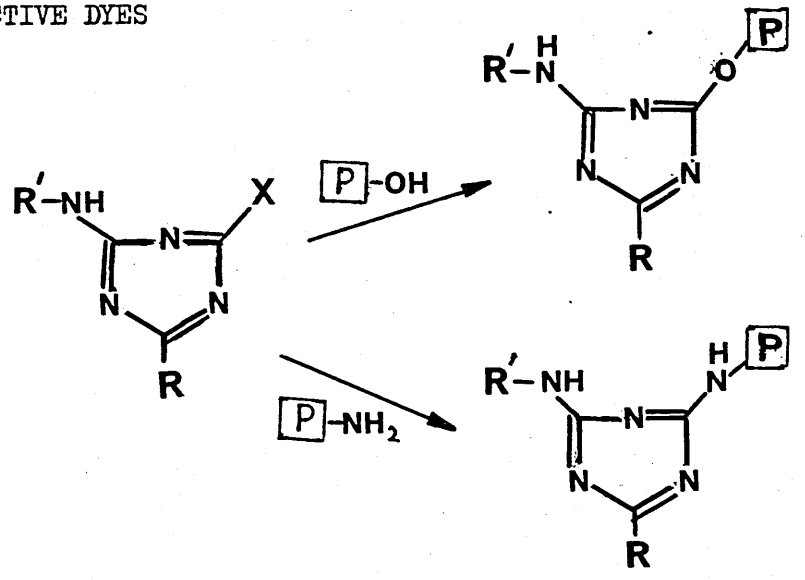
EPOXIDES



ISOCYANATES



REACTIVE DYES



other functional groups present may be capable of binding with separate amino acid residues on different proteins to form other complexes. Studies[372] on plicatic acid using a human serum albumin conjugate (linked to the carboxyl group of the acid by an amide bond) seem to indicate however that the protein in vivo is connected not by this linkage but through one of the groups in the catechol ring (possibly an hydroxyl group.)

The availability of a particular protein at or near the site of invasion into the body by the reactive chemical will clearly determine which conjugate or conjugates are formed. Since a particular agent entering via the lungs is likely to encounter some different proteins to those found when entering via the skin a totally different conjugate is likely to be produced at each site which in turn may lead to different types of reaction being elicited at each of the sites concerned.

Any given carrier protein molecule is likely to have several side groups capable of combining with molecules of the invading haptenic chemical and accordingly the conjugate formed is likely to consist of many haptenic residues joined to a single protein. The total number of residues joined would be expected to be influenced by the relative local concentrations of hapten and carrier protein, the number of available reactive groups of the appropriate type on the protein and their accessibility to the hapten molecules.

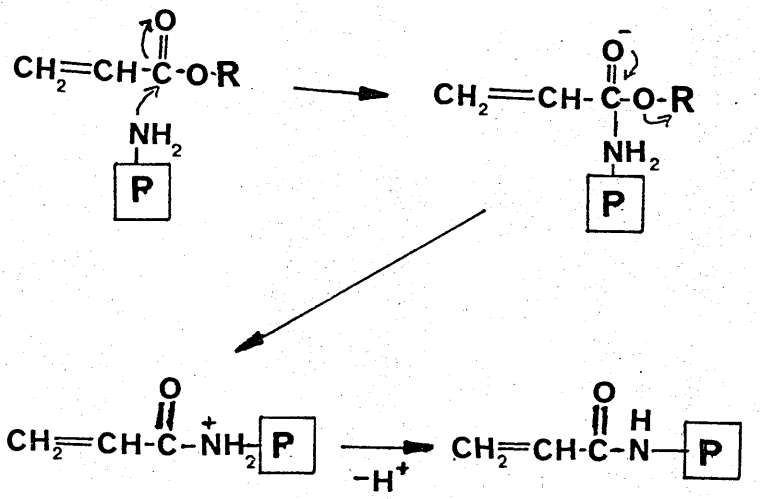
In one study[373] involving a TDI-HSA protein conjugate the molecular ratio of the complex was found to be 34 molecules of isocyanate per molecule of protein. However, in a similar study[374] also using TDI-HSA conjugates it was found that conjugates with 18 to 20 molecules of isocyanate per molecule of protein were more potent antigens than those with greater isocyanate content.

The significance of this is not clear. It is possible that with a large number of haptenic residues on a protein some cross-linking may occur thereby effectively changing the structure of the conjugate and therefore the functional groups capable of acting as an antigenic determinant. Alternatively, a large number of haptenic residues together may reduce the antigenic potential purely through steric hindrance of certain key groups.

Investigations of the mechanism of isocyanate hypersensitivity have been undertaken by several groups[367;382-386] of workers involving animal studies using mice or guinea pigs. Various hapten-protein conjugates have been employed as test antigens to stimulate allergic reactions and to investigate the specificity of antibody produced by isocyanate sensitised workers or test animals. Mono isocyanate compounds have generally been used for antigen formation in preference to diisocyanates to avoid cross-linking of proteins in conjugate formation.

The results generally indicate that the isocyanate group is involved in protein binding via an ureido linkage probably with lysine side chains. Other parts of the isocyanate molecule are involved as part of the antigenic determinant. Additional isocyanate groups (as in the diisocyanate molecule) probably *in vivo* engage in crosslinking proteins and therefore form complex antigenic determinants.

Studies[387] of acrylates and methacrylates in the guinea pig suggest that the presence of an alpha carbon group in the latter molecule decreases its sensitising potential when compared to its acrylate analogue. This may be due in part to steric hindrance affecting the reaction of active groups on the molecule with protein. The linkage to carrier protein would be expected to be formed by displacement of the alkyl group at the alkoxy linkage.



This steric hindrance effect could be acting by decreasing the protein binding potential and so reducing the creation of a potential allergen conjugate in the first place.

The methyl group could also be affecting the reactivity of the molecule generally and its susceptibility to attack by protein side chain groups.

Similar evidence has been found from other studies. Comparison of the reactivity of a series of alpha alkyl substituted cinnamaldehydes towards primary amines showed[388] that the substituted aldehydes reacted very slowly compared to cinnamaldehyde itself. Since the reaction between aldehyde and amine corresponds to that between aldehyde and the $-NH_2$ group of protein this evidence suggests that the substituted aldehydes will not react readily with proteins and that conjugate formation is unlikely. Indeed the substituted aldehydes are found not to be sensitisers. In this case the substituent is thought to reduce the chemical reactivity of the aldehyde group.

Patients sensitised to acrylates in adhesive tape were found[219] to exhibit a broad cross-reaction pattern with acrylic esters yet failed to respond to methyl methacrylate. In particular they reacted readily to 2-ethyl hexyl acrylate but did not respond to the methacrylate analogue. The methacrylate compounds may have only reacted weakly with protein (if at all) and not formed a strong complex which the 'acrylate receptors' in the sensitised patients could recognise.

4.4 Active Sites

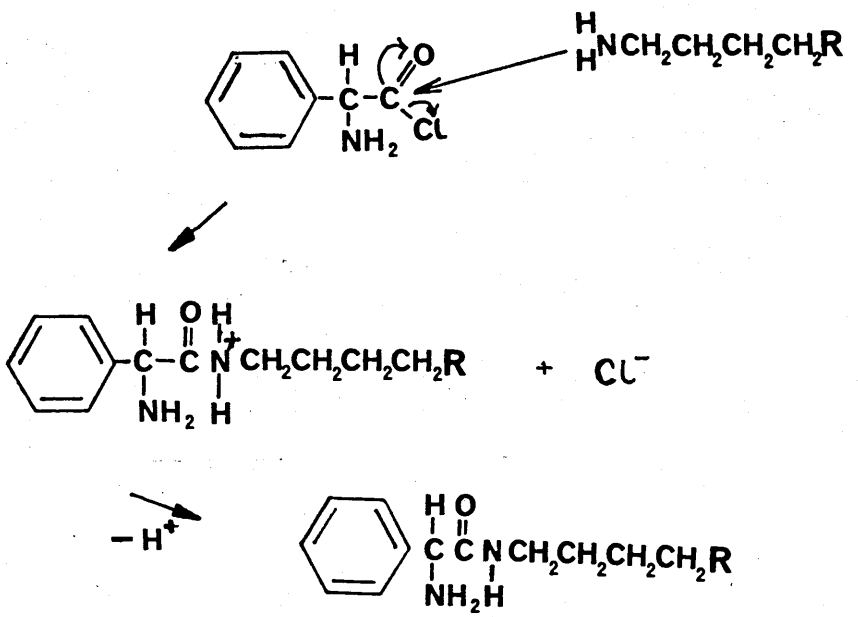
Obviously the site of the chemical linkage between the invading chemical and the carrier protein influences which other parts of the molecule function as the relative

antigenic determinant for the induction of, and subsequent reaction with, specific IgE antibodies in sensitised workers. In the case of very small molecules, the whole of the invading chemical moiety (including groups linking it to protein) as well as part of the protein itself are likely to constitute the antigenic determinant.

With larger and more complex molecules this may not be the case and indeed only part of the chemical may be involved in the active site. Evidence from animal studies[321] on acrylates for example, suggests that the alcohol part of the ester molecule is not involved in influencing the sensitising potential of mono acrylates.

However, since binding of the hapten with carrier protein is an essential prerequisite of the observed allergic response it is probable that groups on the protein constitute an essential part of the active site. Indeed, several studies have shown that the specificity of antibody produced in response to protein conjugates is directed not only against the chemical groupings attached to the protein but also some of the amino acid residues of the carrier protein.

Studies on workers[304] hypersensitive to phenyl glycine acid chloride indicated that the specific antibody produced to the complex formed recognised part of the protein molecule extending beyond the hapten and the lysine residue of the protein molecule through which it was joined.



Similarily in the case of allergy to trimellitic anhydride it has been demonstrated[389] that the antigenic determinant involves at least one amino acid of the carrier protein as well as groups on the hapten part of the conjugate.

In studies[376] on respiratory hypersensitivity in the guinea pig the animals were exposed to an aerosol antigen using p-arsanilic acid and p-tolyl diisocyanate as haptens coupled with ovalbumin or bovine serum albumin. The hapten-specific nature of the pulmonary reactions was demonstrated by a) a response to challenge with hapten-protein conjugates and the lack of response to challenge with protein carrier alone, and b) by reactivity upon challenge with hapten coupled to unrelated heterologous carriers.

The active site and the antigenic determinant formed (which ultimately triggers the allergic response) by one hapten conjugated with a given protein may be similar to that formed by a different hapten conjugated with an alternative protein. The essential point being that the position and pattern of accessible functional groups present on the conjugate and so available to react with antibody need to be the same or very similar.

Indeed, cross reactivity between isophore diamine and isophore diisocyanate has been observed[390]: this would tend to suggest that the part of the molecule reacting with antibody does not contain an isocyanate group, and if the isocyanate group is employed in binding to carrier protein and the amine groups of the diamine undertake a similar role then different protein-hapten links will be formed. However, the active site produced in the two cases could still be similar and may account for the observed results.

The functional groups present at an active site (whether from the hapten or carrier protein parts of the complex) must stimulate a reaction with receptors present on the appropriate circulating memory cells in order for antibody to be produced and an allergic reaction to be triggered. These groups, like those involved in binding to the carrier, will need to be polar thereby enabling them to induce reactions with amino, hydroxyl and similar groups at the receptor site.

Unsaturated carbon chains also appear to be involved as part of the active site in some haptens (eg. acrylates and isocyanates) and not for conjugate formation. Non-reactive saturated carbon chains are unlikely to stimulate reaction with receptors.

The majority of haptens detailed in tables 5 to 9 have more than one functional group thereby providing for at least one group to be involved in binding to carrier protein and one or more groups for acting as the active site. The groups involved in the conjugate formation could still be part of the active site but their influence would be much reduced. However, in the case of formaldehyde, for example, with only one functional group it must be involved in both activities and may induce an antigenic determinant merely by altering the local configuration of the carrier protein.

Diamines may react by cross-linking proteins or parts of proteins to form key groupings which constitute the antigenic determinant.

As indicated above whether one haptenic residue on a carrier protein constitutes one antigenic determinant or whether several haptenic residues on the one protein in close spatial proximity are needed is not clear. With smaller molecules the latter case is more likely since the slight change in protein configuration brought about by joining of an odd group or two is likely to be of marginal significance.

Cross reactivity between related chemicals provides some information about functional groups implicated as antigenic determinants or as part of the active site. In cases of allergic contact dermatitis, patients sensitised to one particular chemical often give positive skin reactions to related compounds. However, it is difficult to conclude that the observed response to the related chemicals is indeed mounted by the same antibodies as those to the original sensitiser or whether the patient is actually sensitised to each of the chemicals being tested. This latter situation may well prevail in susceptible individuals where a particular working environment exposes them not only to the principal chemical but also traces of related chemicals (possibly present as impurities) to which they also become sensitised.

ACID ANHYDRIDES

5.1 Introduction

Anhydrides are widely used in industry. In particular they are one of the principal types of curing agent (hardener) used in the manufacture of epoxy resin plastics. Epoxy resin, made by polymerising a phenol and epichlorhydrin, will polymerise spontaneously at high temperature but the process is expedited by hardeners or curing agents. Curing of the resin is brought about by chemical splitting of the epoxide ring leading to cross linkage between the long chain resin molecules producing three-dimensional structures. External heat is often necessary but the reaction is generally exothermic and during the curing process fumes of resin and curing agent are emitted. (Amines and polyamides are also used as curing agents.)

Phthalic anhydride is used in a wide variety of industrial processes[391]; 60% as plasticiser in vinyl chloride polymerisation; 30% for polyester resin manufacture and in pesticides, essences and perfumes; 10% in the production of alkyd resins in paints and lacquers and in the preparation of benzoic acid. Trimellitic anhydride is also used as a raw material in the manufacture of plasticisers and in the production of resins with hydroquinone and aromatic diamines.

Dermatitis to epoxy resin systems and their components (including anhydride curing agents) is well known[392]. The presentation of dermatitis may be either acute or chronic.

Acute cases show marked oedema of the face and eyelids or of the hands and genitalia, sometimes with large blisters or exudation of serum - suggesting a contact dermatitis from allergy to vapourised resin. Subacute or chronic cases more usually affect the hands and fingers as areas of red, scaly papulovesicular dermatitis but sometimes show lichenification fissuring or psoriasiform appearance - often difficult to diagnose without patch tests and may be due to direct contact with the resin or hardener.

5.2 Respiratory sensitisation

Cases of respiratory sensitisation to four common anhydrides (phthalic anhydride, tetrachlorophthalic anhydride, trimellitic anhydride and pyromellitic dianhydride) have been reported. Formulae and a summary of the observed symptoms are given in table 5e. Case histories of 3 workers apparently sensitised to anhydrides are summarised in figures 8,9 & 10.

Phthalic anhydride is a recognised irritant to the respiratory tract and asthma often develops. Several cases of asthma due to hypersensitivity to the powder and/or its fumes are known - the earliest report being by Kern[305] in 1939. Recently[393] phthalic anhydride has been implicated as one of the causal agents responsible for 'meat wrapper's asthma'.

Tetrachlorophthalic anhydride is also known[310] to cause sensitisation giving rise to a clinical and physiological response indicative of a combined immunologic reaction.

FIGURE 8.

CASE HISTORY OF PATIENT WITH APPARENT RESPIRATORY ALLERGY TO AN EPOXY ADHESIVE CONTAINING PYROMELLITIC DIANHYDRIDE AS HARDENER[148]

The patient had worked with an epoxy resin cured with pyromellitic dianhydride powder, including the mixing of the chemicals and curing of the mixture at 180°C. She had no previous history of hay fever or asthma prior to using the adhesive and did not experience dyspnea on exertion or chronic bronchitis. Whilst she experienced nasal symptoms and wheeze using the adhesive they were much more severe when she mixed it.

Respiratory function tests were undertaken at the workplace. The first reading and one taken 30 minutes later were used as a baseline and subsequent readings expressed as a percentage of it. FEV_1 and FVC were repeated at intervals of 10,20,30,60 and 120 minutes after exposure to the mixed adhesive. The subject declined to be tested when mixing the adhesive. The results are tabulated below.

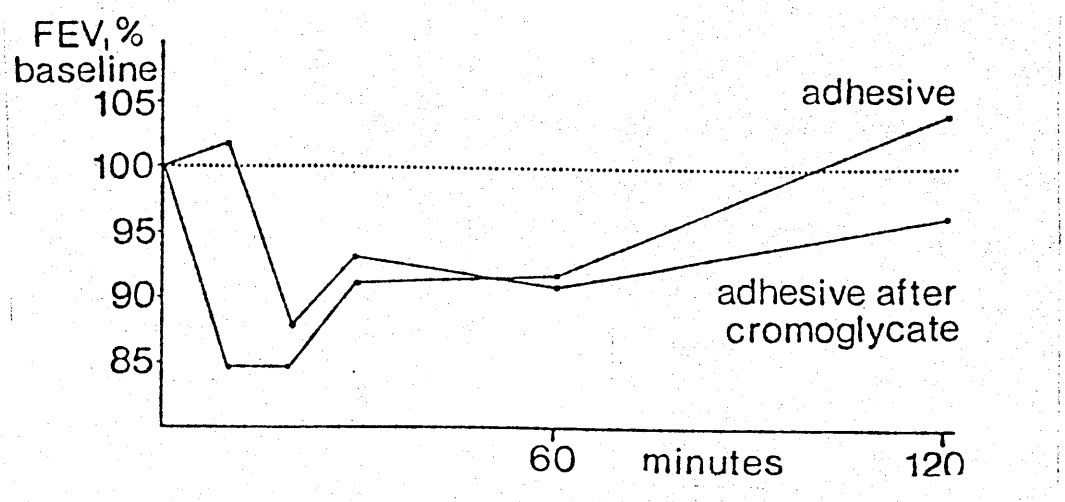
The subject was also tested after inhaling cromoglycate at 20.30 hours the previous evening and 06.00 hours on the morning of the test. The results (as shown on the graph below) indicate little benefit from its use.

FIGURE 8 (continued).

CASE HISTORY OF PATIENT WITH APPARENT RESPIRATORY ALLERGY TO AN EPOXY ADHESIVE CONTAINING PYROMELLITIS DIANHYDRIDE AS HARDENER

USING MIXED ADHESIVE	
Nasal symptoms	+
Respiratory symptoms	+
Time of wheeze (minutes)	45
Fall in FEV_1 (%)	15
Time of fall (minutes)	10
DURATION OF EXPOSURE (MONTHS)	12
ORIGINAL FEV_1 (LITRES)	1.97

The subject was not atopic, did not smoke and gave negative results on prick testing.



Change in FEV_1 as a percentage of base-line values

FIGURE 9.

CASE HISTORY OF PATIENT WITH ASTHMA DUE TO SENSITISATION TO PHTHALIC ANHYDRIDE[37]

The patient worked as a tool setter in a plastics factory specialising in plastics moulding. He had been free of illness until 10 years previous, since when he had minor episodes of acute bronchitis without wheezing, attributed to upper respiratory tract infection. He had smoked 20 cigarettes per day all his working life.

He was responsible for setting up a new machine for encapsulating electrical coils in epoxy resin. The process used a moulding powder of blended epoxy resin with phthalic acid anhydride as curing agent. The powder was fed from a hopper into the mould of the machine around the coil, where it was heated to 150°C. The worker was exposed to large amounts of the fume produced.

He collapsed with severe asthma whilst operating the machine some five months later (although he had no chest symptoms in the meantime) and was admitted to hospital. Asthma recurred when he started work again and followed immediately after exposure to the moulding powder fumes. He was subsequently transferred to a different job.

He was referred for inhalation challenge testing sometime later, and at the time of the investigation had not been exposed to the fumes for 3 months but still experienced occasional wheezing.

FIGURE 9 (continued).

CASE HISTORY OF PATIENT WITH ASTHMA DUE TO SENSITISATION TO PHTHALIC ANHYDRIDE

The results of pulmonary function tests are tabulated below, and the results of the inhalation challenge expressed graphically.

	Actual	% Predicted
FEV_1 (ml)	2880	79
FVC (ml)	5180	104
FEV_1/FVC (%)	55.6	
VC (ml)	4950	99
FRC (ml)	5490	129
TLC (ml)	9190	123

Immediate asthmatic reaction to one breath of fume from phthalic acid anhydride-epoxy resin (●--●) Control with epoxy resin only (●—●) No reaction to a toluene diisocyanate system (●...●)

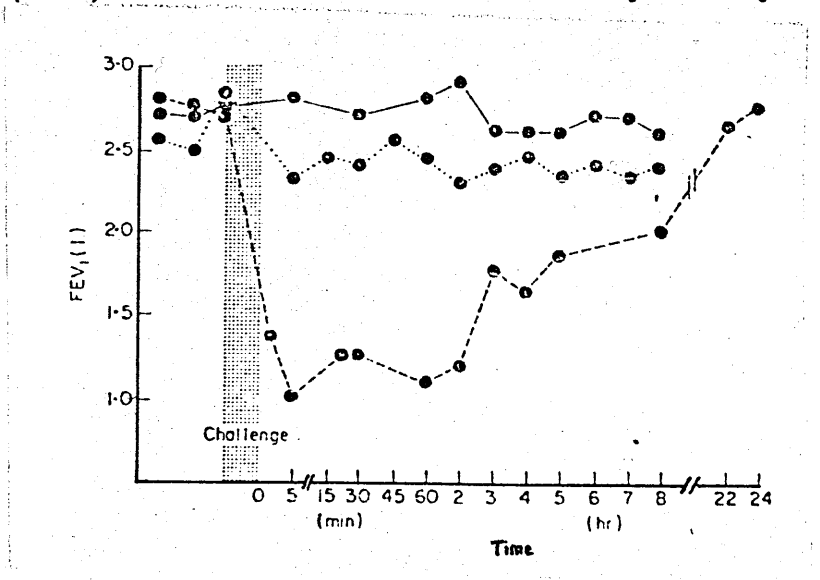


FIGURE 10.

CASE HISTORY OF PATIENT WITH APPARENT RESPIRATORY ALLERGY TO TRIMELLITIC ANHYDRIDE (TMA)[311]

The patient had worked for several years in the bagging area of a TMA plant. After a few months of exposure he developed nasal pruritis, rhinorrea and conjunctivitis to the TMA dust. After a period of years he began to have respiratory symptoms on the job consistent with asthma. He used an isoproterenol inhaler to help him through the work shift. As the symptoms progressed he noted wheezing which persisted throughout the night with cough dyspnea and associated arthralgia, myalgia, chills and fever and was subsequently removed from work.

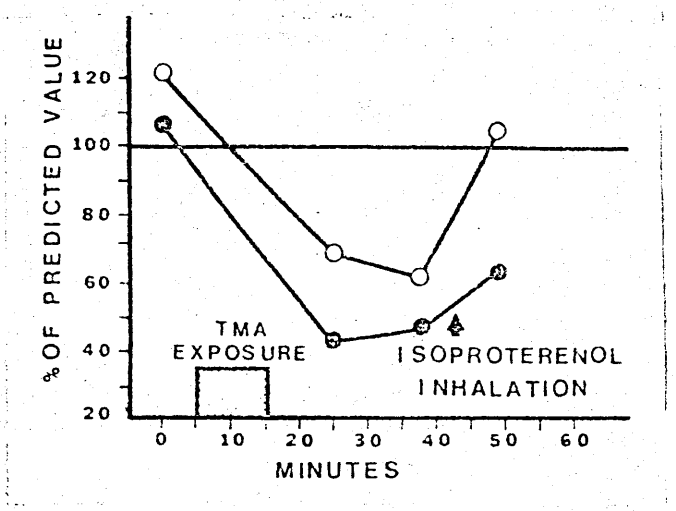
Six months later pulmonary function studies were undertaken both before and after a ten minute exposure in the workplace environment.(TMA dust concentration in this area was 3.3 mg/m^3) His response to this is shown in the graph below. He developed rhinitis and conjunctivitis 5 minutes after onset of exposure and complained of chest tightness and dyspnea shortly thereafter. Physical examination revealed conjunctival erythema, rhinorrea and marked expiratory wheezes throughout both lung fields which had not been present on physical examination before entering the wharehouse. This exposure was not followed by the return of asthma later in the day.

Immunological studies were subsequently undertaken using Trimellitic anhydride human serum albumin conjugate (TMA-HSA) He reacted to this conjugate on skin testing and had 936mg/ml total IgE . Specific IgE and IgG levels were determined by

FIGURE 10 (continued)

CASE HISTORY OF PATIENT WITH APPARENT RESPIRATORY ALLERGY TO TRIMELLITIC ANHYDRIDE (TMA)

polystyrene tube radioimmunoassay and found to be 11200 cpm and 10805 cpm respectively above control levels.



Changes in FVC (o-o) and FEV_1 (•-•)

Serum from the patient was able to transfer immediate hypersensitivity to the skin of the rhesus monkey.

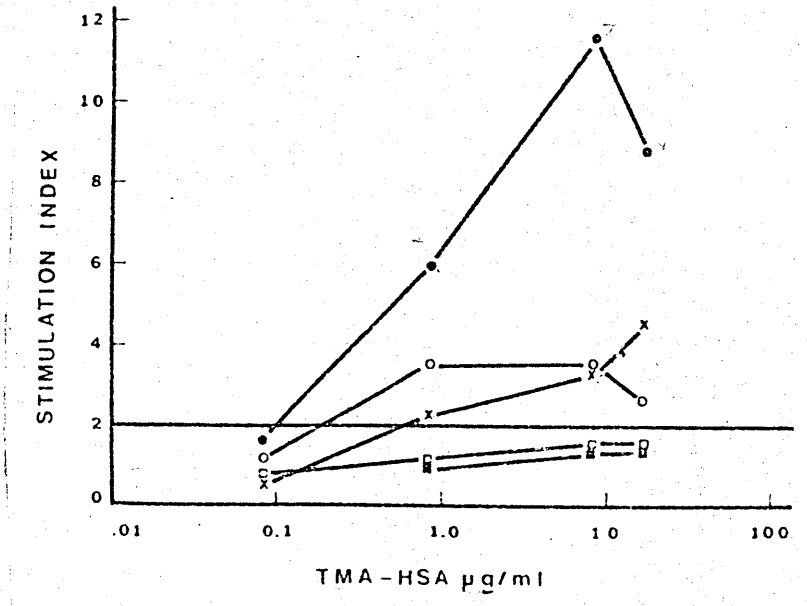
Peripheral blood leucocyte histamine release was determined by incubating cells with the conjugate for 30 minutes, assaying the cell and supernatant histamine and calculating the percentage release. This was found to be 66% with 2 ng of TMA-HSA.

Lymphocytes from the patient were stimulated with varying concentrations of TMA-HSA. Stimulation indices of tritiated thymidine incorporation were calculated by dividing the mean cpm of the stimulated cultures by the mean cpm of the

FIGURE 10 (continued)

CASE HISTORY OF PATIENT WITH APPARENT RESPIRATORY ALLERGY TO TRIMELLITIC ANHYDRIDE (TMA)

unstimulated cultures. The results are shown in the graph below. A stimulation index of greater than 2 was considered significant.



Lymphocyte reactivity in patient (x-x) , two other workers (o-o) & (•-•). Two control subjects have stimulation indices of less than 2 (□-□) & (■-■).

The immediate response is manifested by shortness of breath, wheezing and coughing occuring shortly after exposure this is followed several hours later by chills, malaise, chest tightness and dyspnea typical of the late reaction.

Trimellitic anhydride has given rise to immediate asthmatic reactions in some workers. A late reaction with symptoms resembling extrinsic allergic alveolitis is also recognised and a third response consisting of cough, (which may involve coughing up of blood) dyspnea with pulmonary infiltrates, a restrictive respiratory defect, hypoxaemia and anaemia (referred to as pulmonary-disease-anaemia syndrome) has been reported[311-313]. Immediate type asthma to pyromellitic dianhydride in exposed workers has also been found[148].

These anhydrides all have related chemical structures (table 5a) and consequently it is likely that the underlying mechanism responsible for the allergic reactions observed is similar.

5.3 Antigenic determinant

Anhydrides are reactive chemicalsand readily form an amide or an imide linkage with amino groups of proteins. (See figure 7). It appears that the anhydride inhaled by exposed persons reacts with proteins in the respiratory tract (possibly in the respiratory secretion) to form conjugates which act as allergens. Sufficient quantities of the conjugate formed pass into the tissue spaces and blood stream and

come into contact with the cells of the immune system thereby initiating a response.

Studies[389] on trimellitic anhydride (TMA) using human serum albumin and ovalbumin as carriers indicated that the likely antigenic determinant includes a portion of the protein as well as the trimellitic moiety. However, since both TMA conjugates reacted equally well with antibody it must be concluded that the part of the protein involved is quite small, possibly only 1 amino acid residue, which is common to both these proteins. Human serum albumin is a respiratory protein ovalbumin is not - consequently several other proteins in the body may also be able to act as carriers for the hapten.

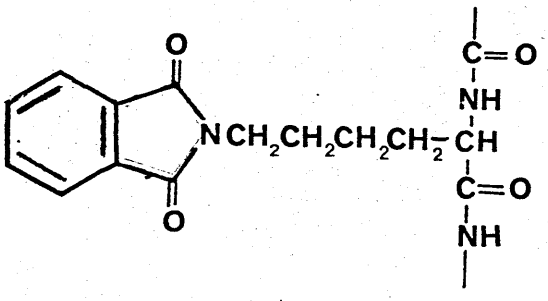
It has been suggested that as many as 30 trimellitic anhydride residues may be attached to the human serum albumin molecule but whether 30 seperate active sites are formed or only one is not clear. Probably 30 amino acid residues are available for combining with the trimellitic anhydride but only a few of these actually constitute active sites. Furthermore the sodium salt of TMA did not completely inhibit IgG antibody[389] to TMA.

However, immunologic studies on workers exposed to both trimellitic anhydride and phthalic anhydride have shown that the antibody responses elicited indicated little cross-reaction between the antibody directed against TMA-HSA or PA-HSA. This would infer that the -COOH group

FIGURE 11.

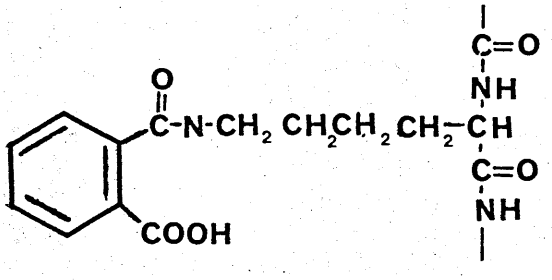
POSSIBLE STRUCTURES OF CONJUGATES WHICH WOULD BE FORMED BY THE REACTION OF PHTHALIC ANHYDRIDE WITH THE EPSILON AMINO GROUP OF LYSINE IN A PROTEIN MOLECULE.

1. IMIDE LINKAGE



phthalic anhydride - lysine moiety

2. AMIDE LINKAGE



of TMA is a key part of the antigenic determinant. It is also possible that this group reacts *in vivo* with other protein side chain groups to form a totally unrelated conjugate.

5.4 Reaction mechanisms

It seems likely from the clinical symptoms observed that both a typeI and a type III reaction are involved in anhydride allergy although both may not be present in individual cases. Although immunological tests have not been undertaken in all reported cases the evidence obtained from those which have would seem to support this view. The initial reaction probably involves IgE antibody and the late one IgG. Indeed TMA-protein conjugates neutralised both types of antibody.

Lymphocyte transformation has been reported[305] in some cases of apparent phthalic anhydride sensitisation inferring a cell mediated mechanism may also be involved. Whilst this has not been shown by other investigators studying respiratory sensitisation to anhydrides, cell-mediated (delayed) hypersensitivity is generally accepted as the causal mechanism for allergic contact eczema (dermatitis) and it is likely that workers developing dermatitis to anhydrides respond via this route.

Maccia[307] et al demonstrated positive scratch tests in patients with respiratory sensitisation to phthalic anhydride after

application of both PA crystals and PA ethanol solution. Patch testing however gave negative results.

It is possible therefore thet phthalic anhydride (and indeed other anhydrides) readily react with proteins in respiratory secretions or in the subdermal tissue to form conjugates which act as antigens for the production of humoral antibodies of both IgE and IgG classes by locally circulating plasma cells. On the other hand, phthalic anhydride directly in contact with skin as experienced occupationally (or in patch testing) is likely to be in contact with different proteins and macromolecules and therefore to form a different type of conjugate. Such conjugates may penetrate the various skin layers in a different way (and possibly at a different rate) acting as an antigen which stimulates cellular antibody production thereby invoking a delayed type hypersensitivity response.

Recent studies[394;395] have implicated the Langerhans cell as 'an allergen trap' which absorbs haptens as they traverse the epidermis and converts them to complete antigens. Furthermore the close association between Langerhans and mononuclear cells in allergic contact dermatitis reactions suggests that they are involved in transferring antigen recognition to T lymphocytes.[396]

The reasons why an immediate respiratory reaction is invoked in some sensitised workers in contrast to a late

or dual response in others is not understood. Clearly the concentration of the agent, its physical form and the duration of exposure will be involved.

Most inhalant allergens in fact do not give rise to contact sensitivity. When they are injected they give rise to an immediate wheal and flare response which may be followed by a late reaction but not by a true delayed hypersensitivity reaction. The immediate response may remove all the effective antigen thereby not allowing a delayed response to be initiated.[397] Evidence from animal studies has shown that immediate allergens injected with an antihistamine will give rise to delayed responses.

CONCLUSIONS AND RECOMMENDATIONS

6.1 Summary of Current Data

Reactive organic chemicals of low molecular weight capable of covalent bonding to groups on amino acid side chains of proteins present in the skin layers or in the respiratory tract are likely to give rise to allergic reactions in susceptible persons who are exposed to them.

The susceptible individual will become sensitised to the chemical at some stage during exposure but is unlikely to manifest any adverse symptoms at the time. Once sensitised the individual concerned will produce an allergic response to subsequent encounters with the chemical even at fairly low concentrations. A response is likely to be produced even if the method of presentation of the chemical in subsequent encounters is different from that initially.

The physical and chemical properties of the invading agent (and its constituents) will influence its site of entry to the body and therefore the likely proteins encountered with which conjugation may occur. Local metabolism of the chemical may occur, modifying its structure and therefore its protein binding ability.

The permeability and mobility generally of the hapten and the conjugate will influence whether only a localised response is triggered or circulating cells and antibodies

are encountered and a more generalised response invoked. Reactions involving cell mediated immunity in preference to those concerning humoral antibody are only likely to occur if the agent is encountered via the general skin layer rather than via the respiratory or gastrointestinal tracts. However, in certain circumstances both mechanisms may be involved.

The production of allergic contact dermatitis (generally cell mediated) rather than allergic asthma (humoral antibody mediated) when certain haptens are introduced to the hands as opposed to the respiratory tract highlights one of the fundamental points in occupational allergy. This key difference in reaction mechanisms is likely to stem from the differences in conjugates formed and the antigenic determinants produced. The accessibility of conjugates to circulating memory lymphocytes of the T and B classes is also likely to be of fundamental importance .

The antigenic determinant stimulating specific antibpdy production is likely to encompass parts of both the invading haptenic chemical and the carrier protein with which it is conjugated and need not be protein specific.

In the case of antibody mediated reactions both IgE and IgG are likely to be involved. The response produced and

the clinical symptoms observed will depend on the secondary mechanisms triggered by them whether complement is involved and on what other mediators or factors are released from co-operating leucocytes. IgE is associated with immediate (type I) reactions with IgG involved in the late (type III) reaction. Whilst these two reactions commonly occur together only one may be present in individual cases.

Irritant, pharmacological and possibly toxic effects of chemicals may swamp allergic responses in persons exposed to relatively high doses of agents to which they are sensitised. Even at fairly low concentrations the observed effects may not be entirely due to allergic mechanisms.

6.2 Sensitisation

Despite the advances in immunology and allergy over the past decades a full understanding of the mechanism of allergy has yet to be achieved. Several key questions require to be answered, the following two in particular :-

1. What predisposes a particular individual to become sensitised compared to others exposed to given potential allergens?
2. Once an individual is sensitised what control mechanisms operate to activate a particular response and symptoms rather than an alternative response which may be displayed by another individual in similar circumstances?

The reasons why certain individuals are susceptible to sensitisation to particular allergens is clearly interlinked with the biological role of allergy generally. Many studies have been undertaken to establish the reasons why allergy has developed. Current evidence[399] suggests that inhalant allergy in particular is a consequence of a genetically determined 'increased' level of local immunity.

Mast cells/basophils and IgE antibodies appear to provide a good defence mechanism against parasitic worms and this may have been an important reason for development of the response. In historical and evolutionary terms this advantage may have outweighed any possible disadvantage from inhalant allergies as currently experienced.

There is also evidence[399], albeit inconclusive, to suggest that cancer patients (particularly those with tumours of mucosal surfaces) have a lower incidence of allergy. Such findings are consistent with the hypothesis that atopy is a consequence of a high level of mucosal immunity.

In the general population there are several different types of persons who do not experience allergic symptoms to a range of antigens:-

i) Those who have not been exposed to a particular allergen.

ii) Those who have been exposed, do not show symptoms or detectable signs at present and who never have had or never will do so.

iii) Those who are going to develop symptoms in the future.

iv) Those who have had allergic symptoms in the past but who have been 'spontaneously' cured.

v) Those who have positive skin tests and detectable serum IgE antibody but deny any symptoms.

All these groups are often referred to as non-allergic and may be used in control studies when comparisons with allergic patients are made, although clearly they are not all necessarily non-sensitised persons. In cases of occupational allergy it is fairly easy to determine whether a given worker has been exposed to a particular allergen and therefore any asymptomatic exposed workers will fall into one of the categories ii), iii), iv) or v) above.

Current evidence[400] suggests that delayed sensitisation and spontaneous cure appear to be antigen specific; that changes in the level of IgG and IgE antibodies generally occur in parallel and that spontaneous cure is not directly age related. Whether the length of allergic responses are in some way related to antigen dose is not known and clearly invites further study. A cellular mechanism for spontaneous cure and perhaps delayed sensitisation may operate involving suppressor T-cells switching off (or on) antibody response to a particular antigen.

Clearly the only truly non sensitised group will be those

falling into category ii) ie. exposed persons who are just non-responders. Further studies involving these persons in any study of exposed workers is essential if the phenomenon of sensitisation is to be elucidated.

6.3 Control Measures

The rapid development of technology currently occurring with an ever increasing demand for new products, particularly in the Plastics field, is undoubtedly provoking the widespread use of chemicals previously of little importance, and the continued synthesis of new chemicals. Since a significant proportion of these chemicals could be allergens such activities are likely to expose many workers to the risk of developing sensitisation, unless appropriate safeguards are taken. Prevention rather than treatment must remain the objective in dealing with occupational allergy, on the one hand by reducing contact with potentially harmful agents and on the other by selection and monitoring of those employed. Prediction of likely sensitisers before use is also important.

A summary of important control measures is given in Table 11. These methods are not mutually exclusive, the greatest benefit will be derived where several are used together.

Ideally substitution of known or suspected sensitisers with 'safer' alternatives is the best practice. However, for many important industrial chemicals there is no satisfactory alternative for the product available.

TABLE 11 : CONTROL MEASURES

1. SUBSTITUTION
   - OF THE PARTICULAR SUBSTANCE
   - OF THE PROCESS INVOLVED
2. ISOLATION (of the chemical from the worker)
   - BY ENCLOSURE
   - BY DISTANCE
   - BY TIME
3. VENTILATION (of the working environment)
   - GENERALLY BY DILUTION
   - LOCAL EXHAUST SYSTEMS
4. PERSONAL PROTECTIVE EQUIPMENT
   - GLOVES, OVERALLS, FOOTWEAR
   - RESPIRATORY EQUIPMENT, MASKS
5. GOOD HOUSEKEEPING
   - PREVENTION OF SPILLAGES, ACCUMULATIONS
   - ROUTINE MAINTENANCE AND TESTING OF PLANT
6. TRAINING AND EDUCATION OF WORKERS
   - ON PREVENTATIVE MEASURES, HAZARDS INVOLVED, GOOD PRACTICES
   - REPORTING OF PROBLEMS, SYMPTOMS

Furthermore questions of toxicity, flammability and explosion hazards will clearly outweigh sensitisation potential when particular chemicals are considered. Of course the likelihood that a given chemical will give rise to sensitisation in exposed workers cannot be clearly predicted although obviously certain indications can be derived from animal studies and pre-screening of atopic subjects. When a particular chemical is found to be a significant sensitiser steps must be taken at that stage to consider whether it can be substituted before the problem develops further.

Wherever possible workers should be divorced from problem chemicals. In many cases reaction vessels, moulding machines etc. can be totally enclosed such that workers operating the process or the machine in question are isolated from the substances involved. Where enclosure is not total the greater the distance between the worker and the plant the better and the location of operating controls should reflect this. Isolation can also be achieved where workers do not enter hazardous areas until chemical reactions have been completed and thus the concentrations, temperatures etc. of particular chemicals will have been reduced.

Unfortunately whilst isolation of production workers can often be achieved other groups particularly maintenance, cleaning and inspection staff, by the very nature of their work, have to gain access to problem areas thereby requiring other control measures.

Airborne concentrations of harmful agents at the workplace can be reduced in most cases by efficient environmental control of dust and vapour. A suitable efficient and properly maintained extract ventilation of the workplace or more particularly as a local exhaust system, is an essential prerequisite. The use of personal protective equipment ranging from filter-type face masks (which are often inefficient, uncomfortable and not tolerated by workers) to positive pressure air hoods and full breathing apparatus will prevent (to varying degrees) inhalation of contaminated factory air. The wearing of appropriate gloves, overalls and boots is also important. Even the use of barrier creams is significant.[401] Complete isolation of workers from the substance in question with handling and observation through the wearing of special containment suits may have to be used in certain cases,[402] a practice well established where bio-hazards are concerned and in the nuclear industry.

Routine on-going monitoring of the workplace checking dust levels, particulate sizes, gaseous concentrations and related factors is vital to ensure that ventilation system provided is working satisfactorily and that other control measures are adequate. Such monitoring must clearly reflect the type of work undertaken and identify potential 'hot spots' in the workplace rather than merely establishing an average ambient level.[403; 404]

Defining a suitable reference level however, is virtually impossible and attempts must be made to obtain as low a concentration of the chemical as possible, preferably at a limit of the order of, or below that which can be detected by modern instrumentation. The introduction of Control Limits, Long Term Exposure Limits (LTEL), Short Term Exposure Limit (STEL) and other measures of 'safe' levels for particular chemicals has been an important step forward in controlling and restricting exposure to hazardous chemicals. However, such levels are principally designed to avoid workers developing acute or chronic conditions (eg. asphyxia, cancer) rather than in preventing sensitisation for which there is practically no safe level in susceptible individuals.

The principal basis for the determination of these limits is toxicity testing of the chemicals of animals and whilst this provides a background of information concerning potential acute and chronic effects on man, in the case of sensitisation and allergic response there are no established animal tests to screen for the existance of sensitising effect on humans. Even if sensitisation can be shown in particular animals there is no guide to its effect in man, indeed the reasons for one individual human being more susceptible to sensitisation than another are not understood. Structure and reactivity of given chemicals provide useful pointers as indicated in this study and more attention could beneficially be given to such matters.

However, in many industries the exact nature of the chemicals involved is often not known and cannot readily be predicted prior to the process starting.

Prevention of exposure must not be confined to the shop floor or stop at the factory gate. Any control measures adopted to protect front line workers must not give rise to hazards to other groups of persons (including the general public). The proper treatment and discharge of extract ventilation systems, the correct laundering of contaminated protective clothing, the safe disposal of both solid and liquid wastes and monitoring of the external environment are equally important. Cases of individuals not actively working with particular substances yet suffering allergic symptoms are not uncommon, and can often be traced to unsatisfactory conditions in these areas.

Transfer of potential allergens to workers clothes and the introduction of such agents into the home and other non-work environments can also pose serious problems. Exposure of the workers themselves is increased thereby prolonging the suffering of sensitised individuals beyond the working day. The likelihood of sensitisation developing in non-sensitised workers is increased and, more importantly, exposure of the worker's family to potential sensitisation and subsequent allergy can occur in such situations.

Comprehensive & continuing education and training of workers together with a high standard of occupational hygiene is essential to eliminate this. The problem is more difficult in non-industrial situations where washing and changing facilities may not be readily available and indeed where the exposed employees may actually work from home (eg. in forestry and farming.) It is imperative that the established attitudes, prevalent in some industries, that suffering is part of the job must be discarded.

6.4 Screening of Workers

Pre-screening of workers for susceptibility to sensitisation is clearly a desirable measure[405]. Unfortunately this is not as simple or advantageous as it might appear. The obtaining of medical questionaires and patch testing using a specific batch of chemicals are established ways of identifying whether workers are atopic. Such procedures are often undertaken when workers are liable to be exposed to dermatitis problems. However, it appears that although an individual may be atopic he is not necessarily any more susceptible to respiratory sensitisation by a given agent than a non-atopic worker. Indeed non-atopic workers are often more susceptible. Furthermore susceptibility to sensitisation to a given agent does not automatically imply susceptibility to sensitisation by other agents. A greater understanding of the reasons why individuals are susceptible and the molecular basis of sensitisation are clearly important if predicting susceptibility and screening of workers is to be successful.

Notwithstanding these problems the routine monitoring of exposed workers is an important function to ensure signs and symptoms of sensitisation in individuals are identified at the earliest opportunity in order that steps can be taken to alleviate the individual's condition and improvements in the control measures operating can be instituted.[194;406] The organisation and establishment of multidisciplinary occupational health services at work-places are clearly fundamental to achieve this task and it is encouraging that many organisations now possess such units. Part time external medical advisers and consultants have a role to play but can never operate with the same effectiveness or provide the same expertise and commitment as an integral occupational health service.

By the time a patient presents with occupationally induced respiratory symptoms preventative measures have failed. It is also obvious that the most effective form of treatment is to remove the worker from the hazardous environment, or at least to relocate him in another part of the plant. In this instance social, financial and other implications must all be considered. Very often suitable alternative employment in areas away from the substance cannot be offered or the worker may refuse jobs for which he is unsuited or which carry lower pay. Premature retirement or dismissal on health grounds may be the only practical alternatives. In certain circumstances sensitised workers may continue to work and remain exposed to the allergen

concerned whilst undergoing some prophylactic treatment such as taking disodium cromoglycate. Clearly this latter course of action should not be taken lightly and may involve the worker in additional problems in the long term. (eg.asthma originally caused by sensitisation to a particular agent may develop into a non-specific form such that the sufferer experiences symptoms even when no longer exposed to the original agent.)

As indicated previously, a speedy correct diagnosis of the worker's complaint is essential. It must involve[407] a review of the patient's past medical history, checking current activities (at work and elsewhere), and thorough medical examination and where possible bronchial challenge with suspected agents, skin testing and laboratory immunological studies. Cases where individuals initially suspected of being sensitised to a particular compound in the work situation subsequently, following more extensive investigation, being diagnosed as allergic to a totally unrelated substance are not uncommon. Once a single case of sensitisation to a given agent has been established in a particular workplace it is more imperative than before to ensure routine monitoring of the working environment is undertaken, that control measures are correctly operating (and where possible to extend them) and more importantly that regular medical screening and examination of exposed workers continues with the aim of identifying additional cases of sensitisation at the earliest stages.

6.5 Availability of Information

A large proportion of the published literature and current data is of little practical use in assessing the aetiology and pathogenesis of occupational allergy since basic immunological studies have not been undertaken in many cases. Provocation tests, determination of total and specific IgE antibody levels and similar studies are key operations which should and must be undertaken if unequivocal diagnosis of allergy is to be made and the causal agent clearly established. The continuing doubts and conflicting data in respect of an allergic mechanism for isocyanate asthma clearly illustrates this point. Whilst the immediate diagnosis of the patient's condition and its treatment must remain of prime concern this should not conflict with the wider objectives of obtaining all possible data relative to sensitisation to a given agent. Indeed the two tasks are mutually beneficial.

There is clearly a need for more liaison and interaction between the various disciplines and professions involved. Physicians intimately involved with the patients under their care often have little scope, inclination or opportunity to discuss individual problems with safety officers, engineers and factory management. Furthermore differences in emphasis, priorities and specialised knowledge amongst physicians can inhibit factory medical advisers, general practitioners, local hospital consultants and research academics from pooling resources and exchanging

ideas not only on individual problems but on the subject generally. Ultimately university and other research workers concentrating on immunological methods or animal studies are likely to become detached from the problems of industry and exposed workers.

Whilst the establishment of local occupational health services by many major employers is clearly an important development more special project teams and interdisciplinary research groups are essential if the full benefits of current knowledge and awareness are to be utilised in achieving good safe healthy working conditions. Bodies such as the Health and Safety Executive, the Employment Medical Advice Service, oocupational health institutes as well as both employers and trades union organisations have important roles to play and must resolve their parochial, political and ideological differences if they are to be fully effective.

Obviously confidentiality on behalf of the patient (and his medical adviser) as well as the employer concerned is important not only in relation to legal and financial matters but also with regard to current public awareness and marketing considerations. Nevertheless such considerations must not inhibit the constructive beneficial dissemination of information which is so important in order to protect others.

Clearly all employers have both moral and legal duties to ensure that not only their workers but all persons likely to be affected by their business undertakings are safeguarded. Residents living in the immediate vicinity of industrial plants and the end users of particular products (including the general public) may all be unwittingly involved. Close liaison between factory operators and residents associations and also between manufacturers and consumer marketing organisations on such health matters is essential.

APPENDIX I

TESTS USED IN ALLERGY INVESTIGATIONS

SKIN TESTS

The two basic skin tests[408] are the patch test (used principally for dermatitis investigation) and the prick test (used principally for asthma and rhinitis).

In the prick test a drop of reagent is placed on a clean dry healthy area of skin (the forearm is a convenient site) and a sharp needle is passed through it at a shallow angle superficially in the skin giving a slight lift to the skin, withdrawing the needle in a direction at right angles to the skin to produce a perceptible 'plink'. The reagent is blotted with a disposable tissue, It is estimated that approximately three ten-millionths of a ml. are introduced into the dermis by this technique. Reading takes place ten to twenty minutes later for maximal effect but delayed reactions may occur from 2 to 72 hours later.

A positive reading is a wheal 1mm or greater in diameter. There may be itching, a red flare and pseudopodial development. (indicative of a Type I, immediate reaction.)

The immediate response may run into a secondary oedematus reaction often strikingly raised above the surrounding skin and extensive, obvious after three to four hours and maximal after seven to eight hours. It is itchy and its borders are ill-defined. (Indicative of a TypeIII, Arthus reaction.)

At forty-eight to seventy-two hours after the secondary reaction has subsided, a third may occur that is erythematous and indurated. (Indicative of a Type IV, delayed reaction.)

The technique of patch testing is simply the application of the test material, in solution or solid on a piece of lint or linen $1cm^2$, to the skin - usually the back but sometimes the arm is used.

The patch test reactions are read at 48 hours after application although reactions may be positive earlier in cases of marked sensitivity. The reactions are graded from 0 to 4+ :-

0	no reaction
1+	erythema
2+	erythema, papules
3+	erythema, papules and vesicles
4+	marked oedema and vesicles.

Low grade reactions (0 to 1 or 2+) are probably not significant. A second reading is usually made ninety-six hours after application. Patch testing can be altered by the topical use of corticosteroids and systemic corticosteroid therapy may suppress most reactions thereby significantly affecting the results.

PROVOCATION TESTS

Whilst oral and nasal provocation tests are used in allergy investigations it is bronchial provocation testing which is a fundamental tool in occupational allergy and has been used extensively in the investigation of patients with asthma and extrinsic allergic alveolitis since 1947.

Bronchial provocation testing is routinely used to evaluate dusts, gases, vapours, and fumes suspected of causing occupational asthma and is also a useful method to monitor the effects of immunotherapy or the effectiveness of drugs. However, although a particular drug may alleviate bronchial response to allergen on provocation testing it may not be effective clinically. Provocation testing is normally undertaken in hospitals where remedial facilities and appropriate treatment are available should they prove neceasary, although these tests are normally considered safe.

The principle method[180] used simulates work exposure to the particular agent and is carried out in an exposure chamber with adequate extraction facilities.

The allergen concerned may be presented in various ways dependant on its physical properties. For example grain and wood dust are best tested by the patient tipping

materials from one container to another whilst vapours from soldering fluxes are readily tested by the subject actually performing the soldering process.

Unfortunately with this test it is difficult to assess the dose of material inhaled by the patient. For many materials in the chamber, however, the concentration can be measured by air sampling and chemical analysis. Where possible the challenge concentration should reflect the known or suspected concentration encountered in the work environment. If the initial test proves negative it is repeated with concentrations 2 to 5 times greater (generally tests repeated at 10 min intervals) until result obtained. Duration of test - 15 to 30 minutes.

Respiratory function is measured 30 minutes and immediately before the bronchial provocation test and then every 5 minutes after the test for 1 hour and subsequently hourly for the rest of the day. It is essential that the tests commence early in the day so that sufficient observations can be made to detect the presence of a late reaction should one occur. Where a late reaction or extrinsic allergic alveolitis is likely to occur (predicted from case histories of the patient etc.) only 1 test per day is undertaken on subsequent days.

It is essential that all forms of medication which the patient may have been receiving are withheld for a period prior to bronchial provocation testing.

An alternative method for the test involves nebulised extracts of the allergen or pharmocological agent being inhaled by the subject through a special form of breathing apparatus. However, this bears little resemblance to natural exposure especially to those agents which normally occur in particle form and furthermore the dose, rate of exposure (rate of administration), presentation of allergen or the site of deposition within the respiratory tract is unlikely to be typical of occupational exposure.

A method of bronchial provocation testing using soluble antigens has been developed by Harries et al.[409]
The test material is inhaled as an aerosol from a Wright's nebuliser through a tight fitting face mask with an oxygen flow rate of 8 litres/minute. Respiratory function is measured every 5 minutes for 20 minutes before the test; every 10 minutes for 30 minutes after the test then hourly for the next 12 hours. A positive inhalation test is registered when a fall in FEV_1 of 15% or more (compared to the control day) occurs within 24 hours of the test or where a rise in temperature, malaise, leucocytoses, development of crackles in the lungs or a fall in transfer factor of 15% or more (compared to control day) occurs within 24 hours of the test.

RESPIRATORY FUNCTION TESTS [410]

These involve the measurement of various lung volumes and generally involve comparisons of the results obtained in healthy subjects with those in patients exhibiting respiratory symptoms especially in asthma.

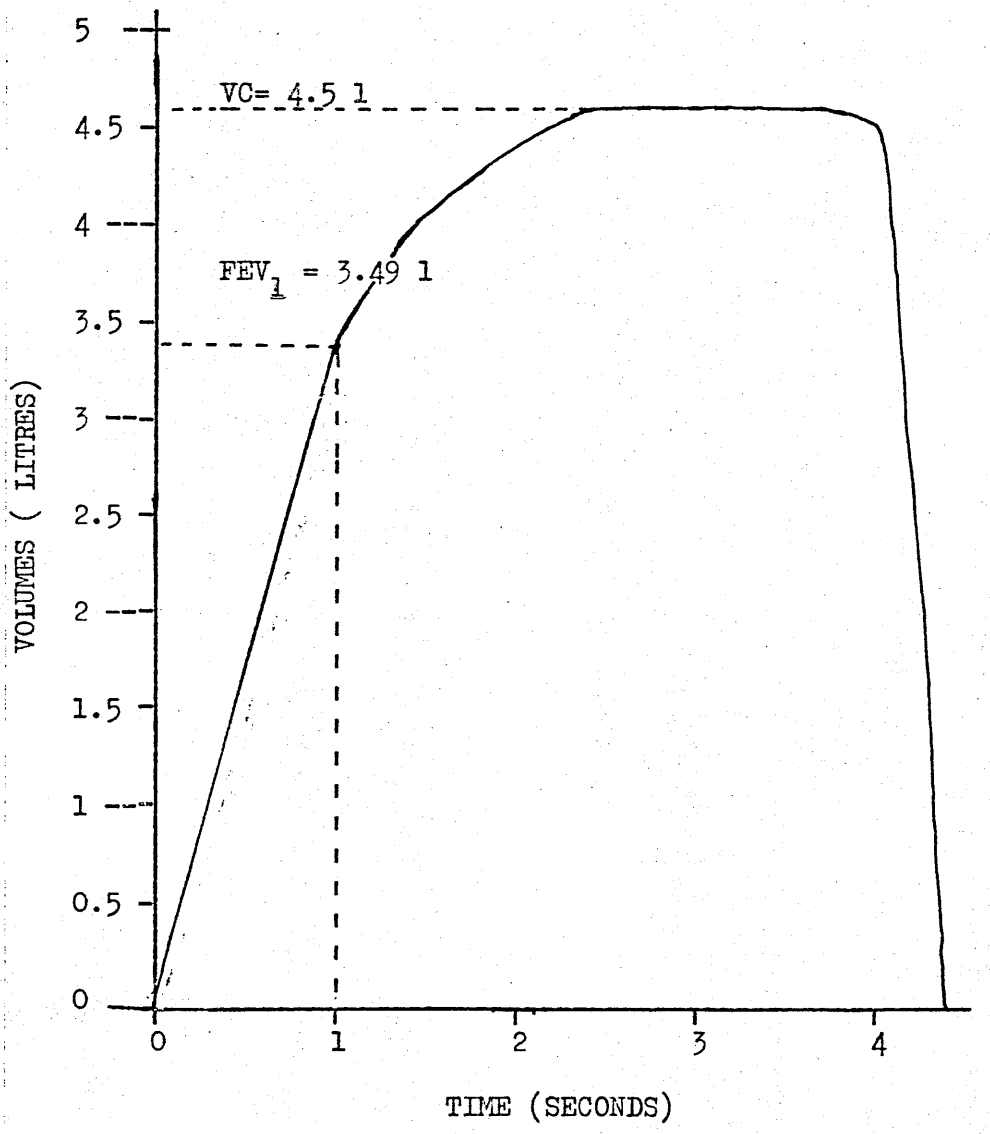
The tests are carried out using various forms of recording spirometers. One of the commonest of these is the vitalograph, an instrument which measures the volume of gas expired during the period of exhalation (at ambient temperature and pressure) and records this against time on a chart. (See figure 12) The subject sits breathing into the apparatus by mouth with his nose sealed. He then takes a maximal inspiration and immediately breathes out forcefully, rapidly and completely as possible into the vitalograph.

The maximal volume of air that can be expelled in one second is called the Forced Expiratory Volume (FEV_1). This reflects the resistance offered by the airways (bronchioles, bronchi, trachea) to the expired air. The total volume expelled is the Vital Capacity (VC). These two records are normally expressed as a percentage ie. $\frac{FEV}{VC}$ %. In normal cases this figure is approximately 80% but it is decreased in patients with airways obstruction.

Vital Capacity is related to the size and development of the subject. (Usually 2.6 l/m^2 in males and 2.1 l/m^2 in females.) It is decreased in older people and in those suffering from

FIGURE 12.

RESPIRATORY FUNCTION TESTS (AN EXAMPLE OF A VITALOGRAPH RECORDING)



$$\frac{FEV_1}{VC}\ \% = \frac{3.49}{4.51} = 77\%$$

certain respiratory diseases eg. polio, respiratory obstruction, pleural effusion, pneumothorax, pulmonary fibrosis, emphysema and pulmonary oedema.

Several other lung volumes and capacities (See figure 13) can also be determined by simple spirometry. The basic recording spirometer consists of a counter-balanced, inverted cylinder moving vertically inside a water-filled khamber so that a variable colume of air or gas is trapped under the cylinder. The cylinder is connected to a recording drum (Kymograph) such that when the lung volume increases in inspiration, the volume of the gas in the spirometer is reduced and the pen on the chart rises; conversely the pen falls with expiration.

The subject breathes through the mouthpiece in a closed circuit with the spirometer and his nose sealed. The instrument records the volume of air movement against time and a record of normal breathing and of deep inspiration and full expiration is made. The following lung volumes can then be calculated:-

a) Tidal Volume (V_T) - the amount of gas inspired or expired during a single normal breath

b) Inspiratory Reserve Volume (IRV) - maximal amount of gas that can be inspired after a normal inspiration

c) Inspiratory Capacity (IC)=IRV + V_T

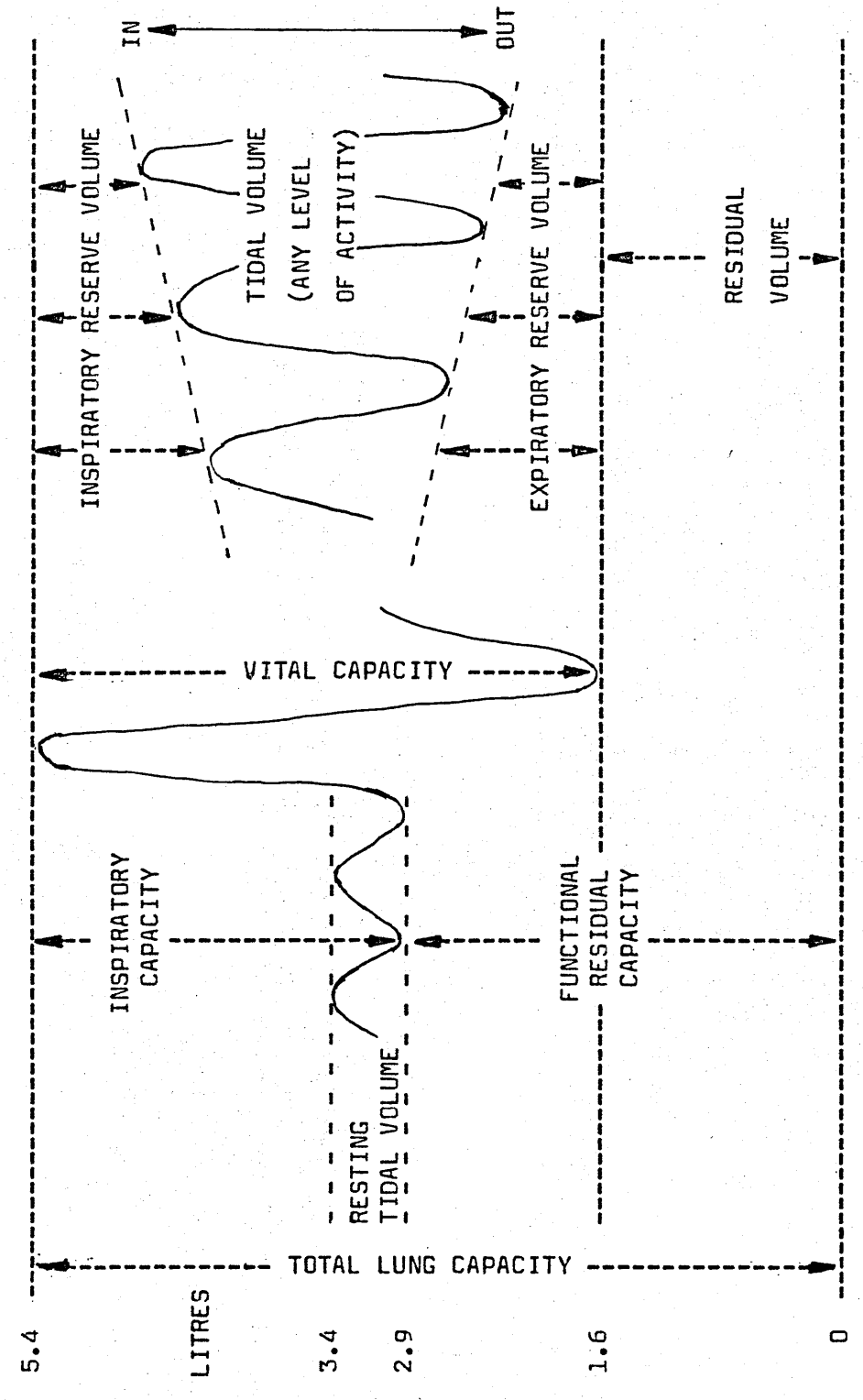
d) Expiratory Reserve Volume (ERV) - maximal amount of gas expired from the end-expiratory position

e) Vital Capacity (VC) = IC + ERV

FIGURE 13.

LUNG VOLUMES AND CAPACITIES

A representation of a recording obtained by a spirometer to illustrate the sub-divisions of the lung volume. The figures on the left are the average values for an adult man.



Measurements of Residual Volume (RV), Functional Residual Capacity (FRC) and the Total Lung Capacity (TLC) have to be determined by a separate technique - the closed circuit helium dilution method is often used. Residual volume may however be calculated using the following arbitary formulae :-

Males RV (ml) = 26 x age (years) + height (inches)
- 11 x weight (pounds) - 4570

Females RV (ml) = 10 x age + 1320

Hence FRC = ERV + RV and TLC = VC + RV

LABORATORY TESTS

Determination of total serum IgE, a routine clinical procedure, is normally undertaken by a form of Radio-immunoassay (eg.) the Double antibody inhibition radio-immunoassay or the Radioimmunosorbent technique (RIST). These tests which are fairly sensitive involve antibody-antigen interaction in which one of the reactants has been labelled with an appropriate radioactive isotope. The key step involves competition between labelled and unlabelled forms of one reactant (in this case IgE) for binding sites on the other reactant (anti IgE). The labelled antigen is usually present in slight excess over the antibody. Since the capacity of antibody to bind antigen is limited addition of serum containing unlabelled antigen will cause a decrease in the amount of labelled antigen that is bound.

In the double antibody inhibition RIA the test serum is mixed with rabbit anti-IgE and the radiolabelled IgE added. Goat anti-rabbit is then added to precipitate the rabbit immunoglobulin and after washing the radioactivity in the precipitate is counted.

The RIST uses a solid phase for one of the reactants therefore a second antibody is not required. Particles of activated cellulose or similar material are used to bind anti-IgE preparation. The mixture is then centrifuged, washed and the radioactivity on the immunosorbent counted. The amount of label bound to the insolubilised antibody is therefore inversley proportional to the amount of IgE

in the test serum.

The quantity of IgE present in the test serum can then be found by reference to a 'standard curve' (ie.) a graph showing the percentage of labelled IgE bound as a function of the amount of unlabelled IgE present. The curve having been constructed from data obtained by performing the assay using samples of unlabelled serum in which the concentration of IgE present is known.

The Radioallergosorbent Test(R.A.S T.)

The level of antigen-specific IgE can be determined by this method. Specific allergen is coupled with an insoluble matrix (eg. cellulose beads) and the particles allowed to react with the test serum. IgE antibody with specificity for the coupled antigen will bind to the particles. A further incubation is performed by adding radiolabelled anti-IgE. The percentage of the added counts bound to the matrix is a measure of the antigen-specific IgE in the test serum.

RAST correlates quite well with clinical allergy but precise correlation with skin tests awaits antigen standardisation. Clinical scores are obtained by comparison with RAST results with strongly positive reaginic sera: A 4+ RAST precipitates as much radio-labelled antibody to IgE as does a 1:1 dilution of reference sera; a 2+ RAST

precipitates as much as a 1:4 to 1:25 dilution and a negative RAST indicates less reactivity than a 1:50 dilution of reference sera. False positive results are rare with this technique. Clinically the RAST may provide an alternative to skin tests in persons with dermagraphism or severe dermatitis, in apprehensive adults or small children.

Furthermore the RAST allows a safe diagnostic approach when intradermal (eg. bee sting) or provocation tests may be hazardous, or when the withdrawal of drugs (eg. anti-histamines) inconveniences the patient. Another advantage is the possibility of being able to study physiological fluids other than serum (gut or nasopharangeal secretions for example). The fluids could be stored, as could serum, for future analysis at a convenient time.

The RAST has been useful in demonstrating IgE antibody to such diverse agents as ragweed, grass, pollens, nuts, Hymenoptera extracts, insulin and the penicilloyl antigens of penicillin.

Red-cell linked antigen-antiglobulin reaction (RCLAAR)

This technique makes use of red blood cells as indicator particles. Red cells are ideal indicators of antigen-antibody interactions because they are less liable to adsorb proteins non-specifically than are other indicators.

The antigen is first coupled to rabbit antibody directed against the red cells (the use of this reagent prevents excessive disturbance of the red cell membrane and clumping which would occur if the antigen was coupled to them direct.) The reagent formed when incubated with the indicator cells links to them by means of the antibody without damage of the membrane. If the cells coupled to the reagent are then incubated with serum containing antibody with specificity for the coupled antigen combination takes place. Antiglobulin specific for the heavy chains of the antibody used is added to agglutinate the red cells. (This enables specific antibody of IgE, IgG and other immunoglobulin classes to be separately determined.)

Antigen binding radioimmunoassay (or radioimmunoprecipitation)

A technique which enables IgG, IgA and IgE antibody in a given serum sample to be determined in parallel. Using low concentrations of allergen the relationship between different classes of antibody is accurately reflected. Furthermore since in vivo exposure to allergens is probably at low concentration antibodies measured in the presence of low concentrations may reflect the biologically relevent antibody.

Serum samples are incubated with radiolabelled allergen and carrier protein for 4 hours. Goat anti-IgE (or IgG or IgA) is added and left overnight to precipitate then the precipitate is washed and the radioactivity counted.

The count is directly related to the quantity of specific immunoglobulin in the serum.

The assay however requires large quantities of IgE and IgE myeloma serum (as carrier protein) and so is not normally used in preference to RAST for routine IgE determination.

APPENDIX II

GLOSSARY

ANAEMIA Bloodlesness - in particular shortage of haemoglobin in red blood cells characterised by signs and symptoms of oxygen lack.

ANAPHYLAXIS An extreme form of allergy whereby the subject reacts very sharply. In severe cases the bronchi go into spasm and death may result unless prompt treatment with adrenalin is given. Commonly used to mean a type 1 allergic reaction.

ASTHMA A respiratory disease characterised by recurrent attacks of difficulty in breathing usually accompanied by wheezing, cough and a sense of constriction of the chest. It is due to spasm of the muscular fibres in the walls of the bronchioles reducing the size of the airway and impeding respiratory airflow especially when breathing in.

ATOPY The capacity of an individual to develop type 1 allergy to common environmental materials which is demonstrable by skin or serological tests without necessarily being linked to the presence of clinical symptoms. It appears to be hereditary and involves genetic factors but is not fully understood.

BASOPHIL A type of white blood cell containing granules which stain blue/black. They are found in much fewer numbers than either neutrophils or eosinophils. Their function is poorly understood but they are implicated in histamine release in immediate type hypersensitivity - analogous to that found with mast cells.

BRADYKININ A polypeptide that causes the walls of blood vessels near the site of an injury to be more permeable allowing fluid to escape into the tissues. It is also capable of inducing contraction of smooth (involuntary) muscles.

CEILING LIMIT A term used when defining occupational exposure limits, (sometimes referred to as the Threshold Limit Value-Ceiling) indicating the concentration that should not be exceeded even momentary.

CONTROL LIMIT The level of an airborne contaminant, averaged over a specific time period,above which personal exposure is oonsidered to be unacceptable.

DISODIUM CROMOGLYCATE A non-corticosteroid drug which inhibits the release of histamine and SRS-A from sensitised human lung. It is not antagonist of histamine or SRS-A and is not anti-inflammatory. Effective in many patients in preventing but not reversing experimentally induced allergic or exercise associated asthma.

DYSPNOEA Undue breathlessness and abnormal awareness of the effort of breathing.

EOSINOPHILS White blood cells containing large granules readily stained with the red dye eosin which originate from the bone marrow. Increase in the concentration of these cells above 4% of the total white blood cell numbers occurs in several conditions including some allergies. They accumulate at the sites of antigen/antibody reaction in response to specific chemotactic factors liberated locally. Immune reactions involving IgE are particularly likely to attract eosinophils. They are implicated in processing and cell to cell transfer of antigen breakdown products and their phagocytic potential is well documented.

ERYTHEMA Abnormal reddening of the skin. Erythema with rise in temperature generally heralds onset of fever whereas erythema without rise in temperature is most commonly the result of allergy.

HEMOPTYSIS Coughing up of blood from some part of the respiratory tract.

INDURATED Hardened or calloused.

LICHENIFICATION An area of thickened and hardened skin in which the normal skin markings are visibly accentuated. This condition is usually due to chronic inflammation resulting from scratching.

LYMPHOCYTE A type of white blood cell (leucocyte) involved in adaptive immune responses particularly in the recognition of antigen and the specificity of all responses made against it. Small lymphocytes carry the information for binding to antigen and a vast number of different specificities exist in the whole lymphocyte population. They are capable of several quite distinct activities ranging from the ability to differentiate into antibody producing cells to being cells directly involved in cell-mediated immunity. Two distinct types are found: the so called Bcells from the bone marrow involved in antibody production, and the T cells which develop under the influence of the thymus gland and are involved in cell mediated immunity. Cooperation between the two types occurs in several reactions.

LYMPHOKINES Chemical substances which affect certain types of cell (including macrophages and various white blood cells) in a multitude of ways in order to augment a particular immune response. Commonly secreted by lymphocytes.

MACROPHAGES Large cells circulating in normal individuals, capable of carrying out several functions. One of the most important of these being phagocytosis - ingestion and digestion of foreign material. They contain packets of enzymes capable of bringing about proteolysis of such material.

MAST CELLS Cells found in connective tissue filled with coarse granules. They secrete heparin (anti-clotting

agent of blood) and histamine. Release of histamine in particular is triggered in type 1 allergic reactions by a mechanism not fully understood but which involves binding of IgE antibody to receptors on the cell prior to antigen/antibody reaction. Histamine release can be initiated by other mechanisms involving mechanical or chemical irritation.

NEUTROPHILS Phagocytic cells present in the blood, more motile and effective phagocytes than macrophages. Neutrophils form one of the first lines of defence in the body being one of the first cells to arrive on the scene in large numbers at the site of entry of foreign material into the body. They may be attracted towards target material by chemotaxis.

OEDEMA Abnormal accumulation of watery fluid in the body tissues and cavities.

PAPULE A pimple or small projection raised above the surface of the surrounding skin. Hence PAPILLARY.

PHAGOCYTOSIS The process of ingestion and digestion of foreign material by certain cells, principally macrophages and neutrophils. Phagocytosis occurs throughout the body but the liver is a principal site. An important part of native immunity as well as in specific reactions of adaptive immunity.

PROPERDIN A protein present in the serum and body fluids participating in the complex system of natural immunity. Its activities include bactericidal action against gram-negative bacteria, neutralisation of some viruses and protection against fatal radiation sickness.

PROSTAGLANDINS A series of related fatty acids found in various parts of the body and which act as local hormones. They have the ability to lower blood pressure and can inhibit the activity of catecholamines in mobilising free fatty acids.

PRURITIC Irritant or itchy.

PSORIASIS A fairly common skin disease characterised by the formation of red patches which are covered by fine silvery scales. Hence PSORIASIFORM.

PURULENT Containing or discharging pus.

RHINITIS The generic term for inflammation of the mucous tissue ofthe nose. When it is allergic in origin it is usually referred to as hay fever. The symptoms are sneezing, rhinorrhea, nasal obstruction and itching of the nose, palate and pharynx.

SHORT TERM EXPOSURE LIMIT (STEL) An occupational exposure limit aimed primarily at avoiding acute effects or at least reducing the risk of occurence. They are normally expressed as 10 minute time weighted average (TWA) concentration. The units being parts per million (ppm) or milligrams per cubic metre of air (mg/m^3). These limits are considered to represent good practice and realistic criteria for the control of exposure, plant design, engineering controls and, if necessary, the selection and use of personal protective equipment. STEL and Long Term Exposure Limits (LTEL) are listed for a large range of materials in a Health & Safety Executive Guidance Note. Sensitised individuals may well react to exposure to minute levels of substances (acting as allergens) well below these listed concentrations.

LONG TERM EXPOSURE LIMIT (LTEL) An occupational exposure limit concerned with the total intake over long periods intended to protect against the effects of long term exposure or reducing the risks to an insignificant level. They are normally expressed as 8 hour time weighted average concentrations.

URTICARIA An allergic condition characterised by the rapid appearance of weals and blisters on the skin usually lasting for only a few hours and accompanied by intense itching. Thought to be due to release of histamine leading to raised vascular permeability and local acccumulation of fluid in the dermis of the skin. Urticaria may also be produced by non-immune reactions.

VASODILATION Expansion of a blood vessel.(Reverse referred to as vasoconstriction.)

VESICLES Small blisters occurring as an eruption on the skin or mucous membrane conventionally not larger than a pea. The horny layer of the skin is raised by exudation of clear or turbid fluid to form a rough hemispherical protrusion sometimes surrounded by a red inflamed zone. Hence VESICULAR.

APPENDIX III

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